VOL. 73 FEBRUARY, 1957 NO. 2

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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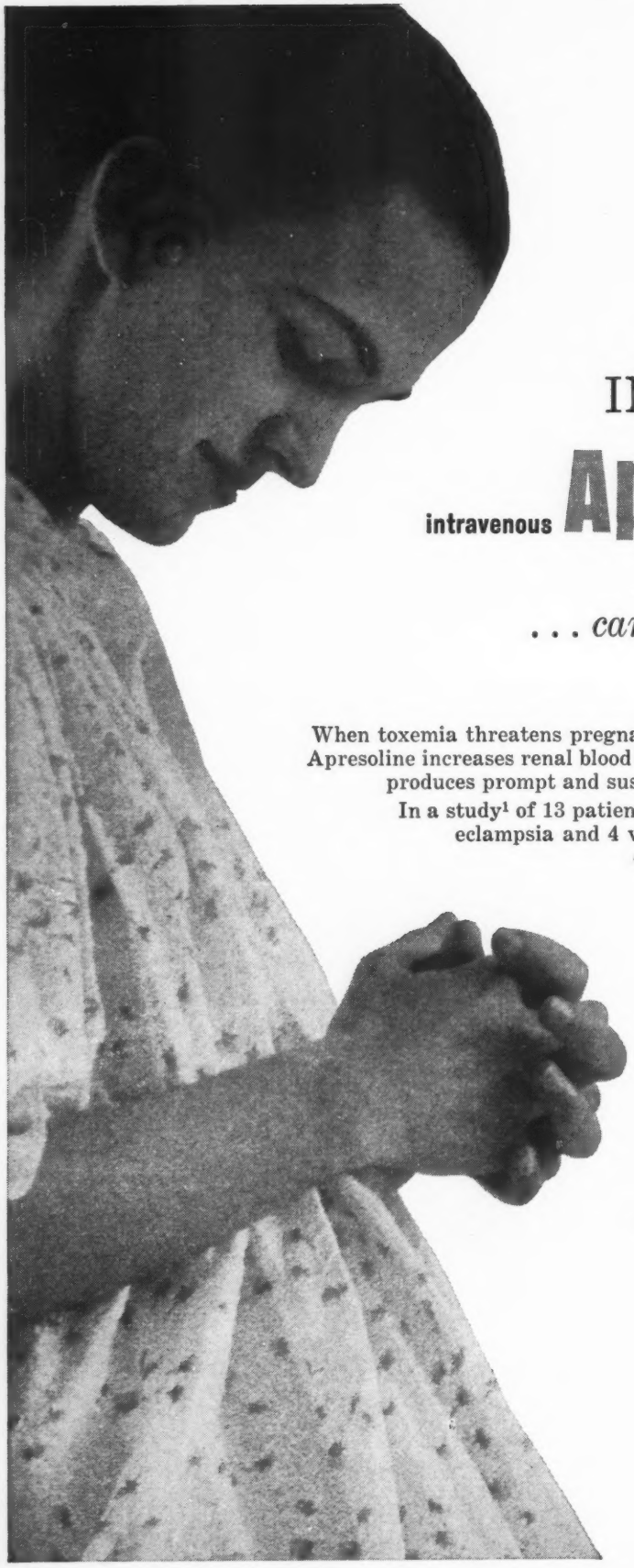

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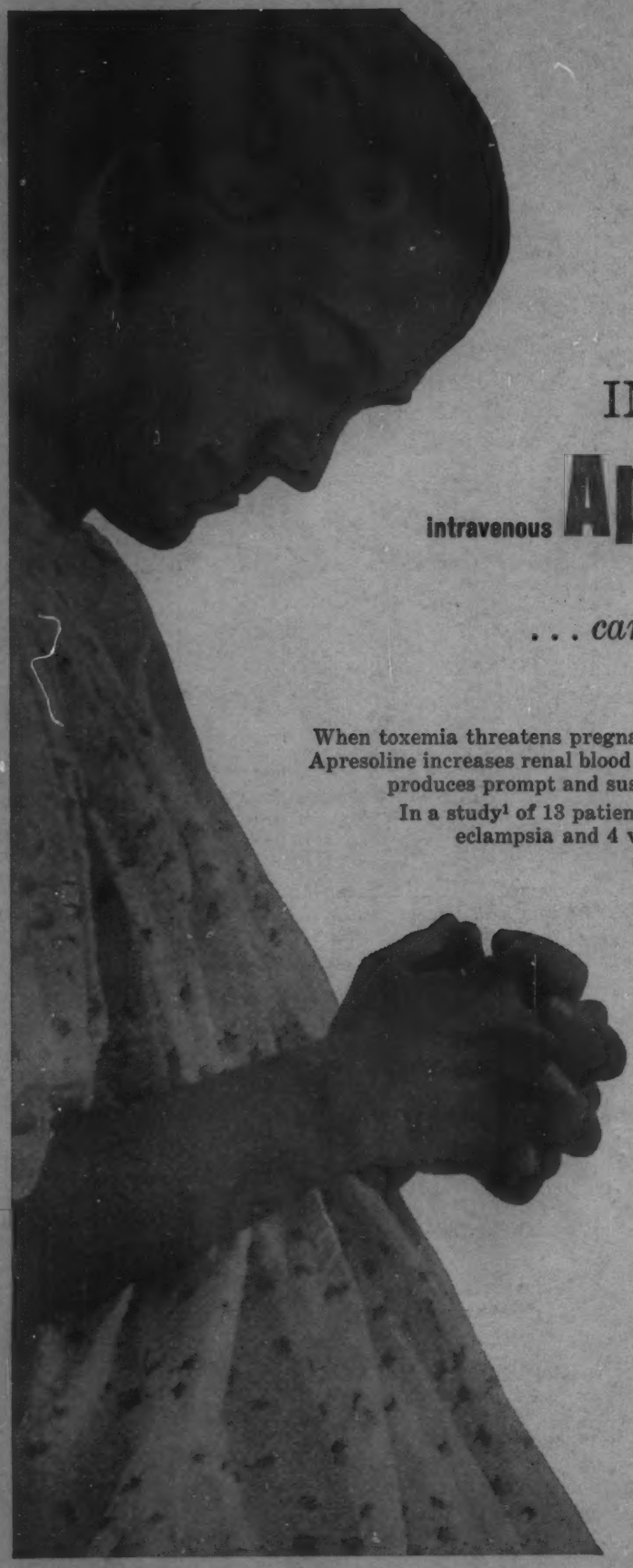

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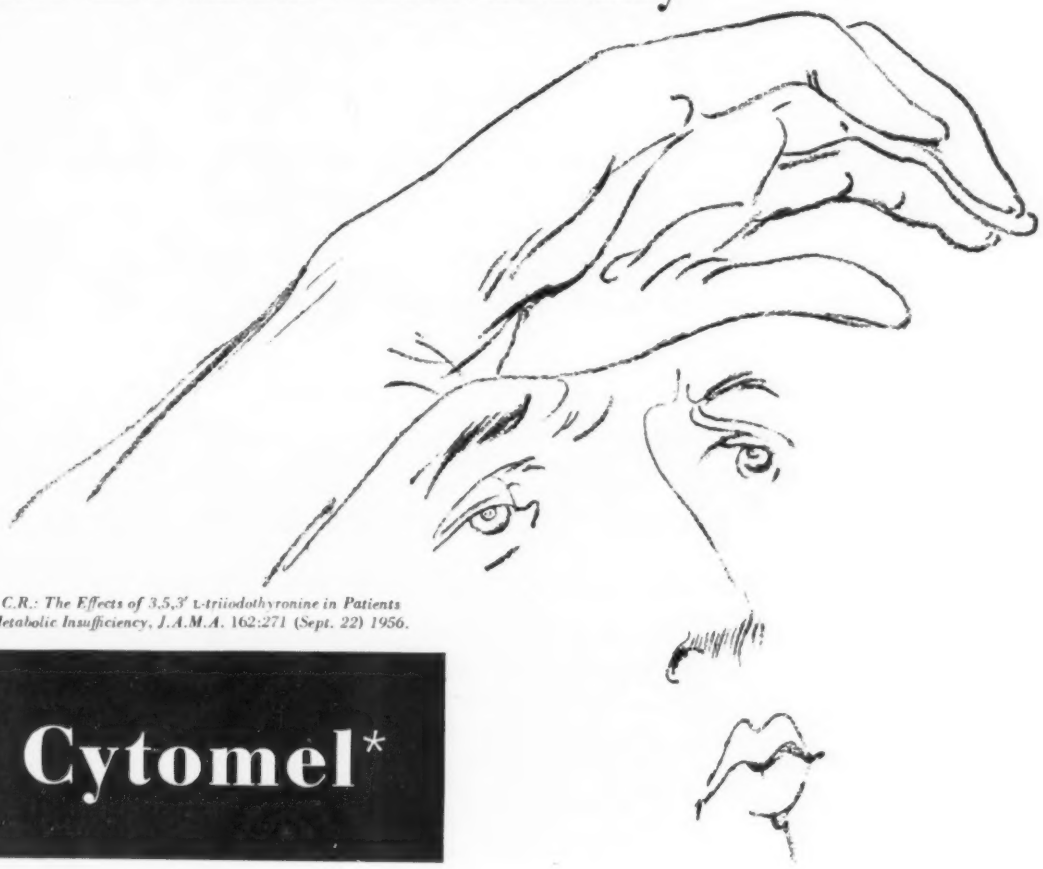

1. Tittle, C.R.: *The Effects of 3,5,3' L-triiodothyronine in Patients with Metabolic Insufficiency*, J.A.M.A. 162:271 (Sept. 22) 1956.

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PUBLISHED BY THE C. V. MOSBY COMPANY, 3207 WASHINGTON BLVD. ST. LOUIS 3, MO.

Entered at the Post Office at St. Louis, Mo., as Second-Class Matter.

Published Monthly. Subscriptions may begin at any time.

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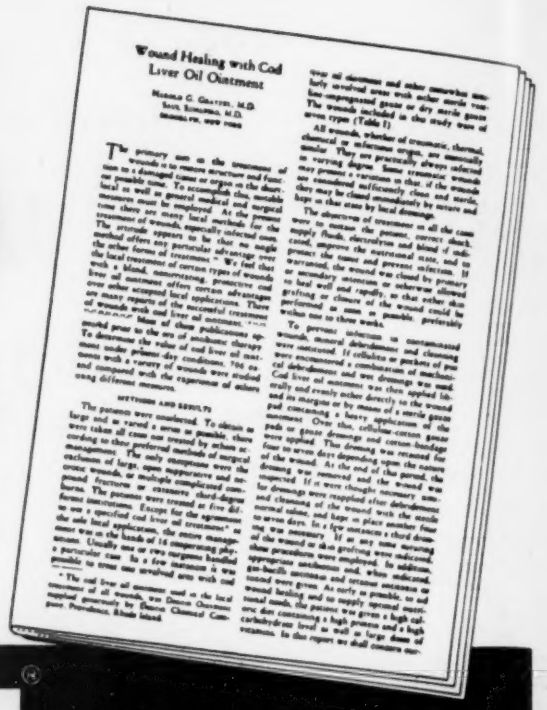

Wound Healing with Cod Liver Oil Ointment

DESITIN® ointment

promotes "early, clean and healthy healing"

in

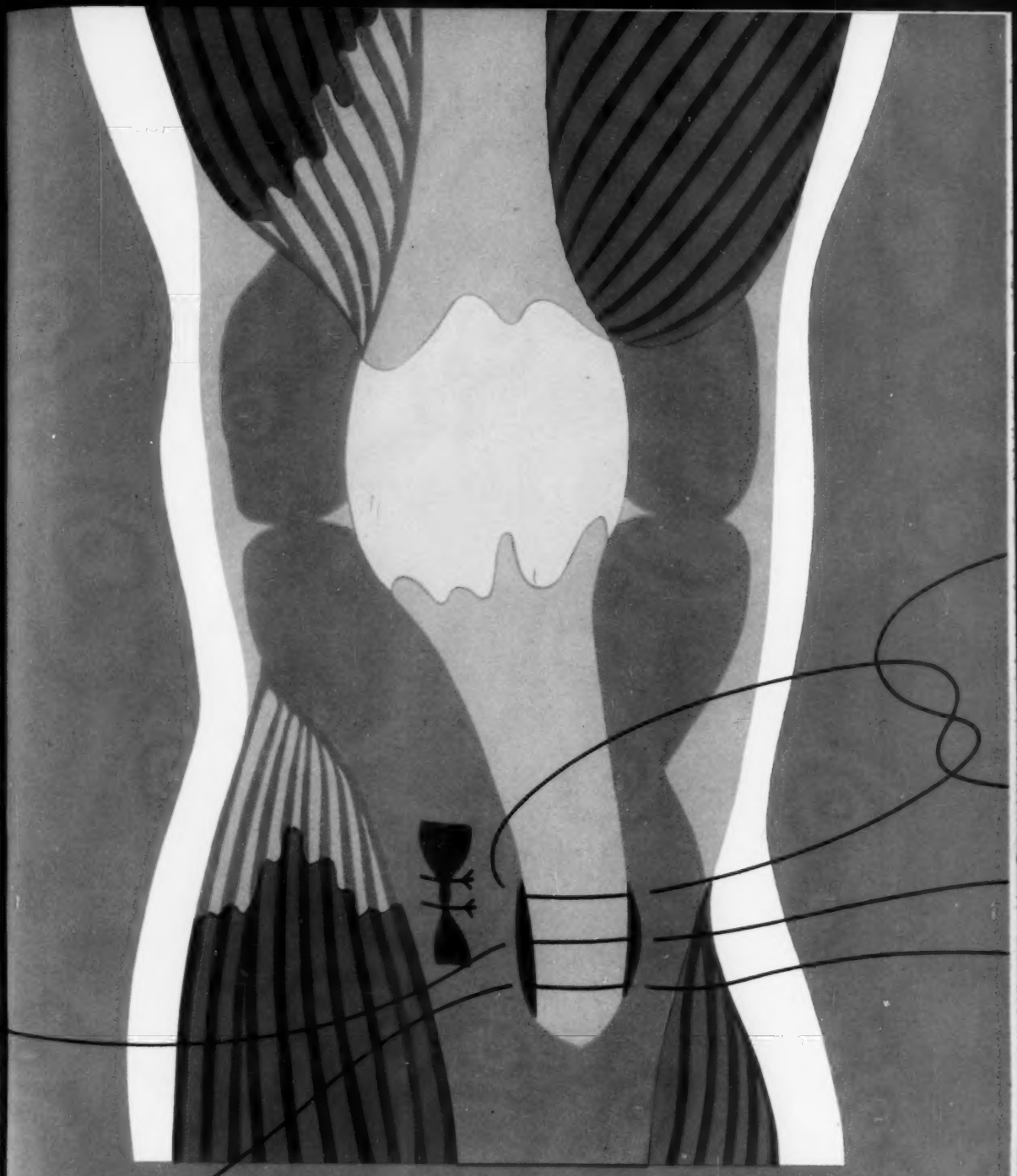
- traumatic and infectious wounds
- burns (first, second, third degree)
- abdominal fistulae and wounds
- pressure sores and ulcers
- pilonidal cysts and sinuses
- ano-rectal wounds • chest wounds

This confirms previous findings regarding the efficacy of soothing, protective, non-irritant Desitin Ointment—rich in cod liver oil—to accelerate healing in many other skin conditions . . . diaper rash, ulcers (decubitus, varicose, diabetic), etc.

samples *and new reprint*[1] *on request.*

DESITIN CHEMICAL COMPANY
812 Branch Ave., Providence 4, R. I.

1. Grayzel, H. G., and Schapiro, S.: Western J. Surgery, Obstet. & Gyn., Oct. 1956.



setting new standards

ETHICON®

sutures

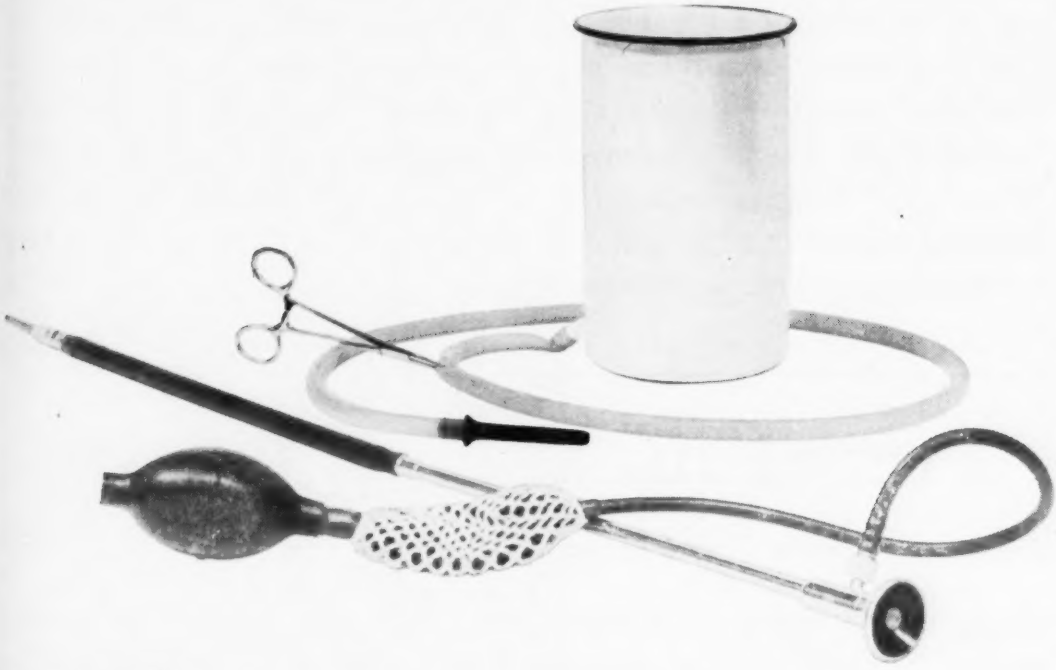
ETHICON®

. . . part of *every illness*

ANXIETY

is part of

GASTROINTESTINAL DISORDERS



In every patient . . .
a valuable adjunct
to the customary therapy

Supplied: Tablets, 400 mg., bottles of 50.
Usual Dose: 1 tablet, t.i.d.

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MEPROBAMATE

(2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate)

Licensed under U.S. Patent No. 2,724,720

anti-anxiety factor with muscle-relaxing action

RAPID HEALING IN VAGINAL SURGERY PROMOTED BY LOCAL ESTROGEN THERAPY

In the postmenopausal patient, local estrogen application before and after plastic vaginal surgery promotes proliferation and vascularity of the epithelium, thus restoring the atrophic and friable mucosa to a more normal state. This facilitates the surgical procedure as well as favors more rapid healing. Doyle[1] suggests the use of "Premarin" Vaginal Cream 7 to 10 days prior to surgery. Hamblen[2] recommends local estrogen therapy for about 10 days before, and 10 days after, intervention.

Treatment of Senile Vaginitis is Simplified

According to Doyle, local estrogen therapy provides "a valuable therapeutic constituent in the management of vaginitis and vaginal infections, regardless of etiology."[1] This method affords "an almost immediate healing and soothing effect."[3]

"Premarin"® Vaginal Cream

"PREMARIN" VAGINAL CREAM in a nonliquefying base, is standardized in terms of the weight of active, water-soluble estrogen content expressed as sodium estrone sulfate (0.625 mg. per gram). Presented in a combination package No. 874 — 1½ oz. tube with specially designed calibrated applicator; also refill available.

Complete information may be obtained by writing to Ayerst Laboratories, 22 East 40th Street, New York 16, N. Y.

1. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 2. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657. • 3. Doyle, J. C.: California Med. *71*:15 (July) 1949.

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

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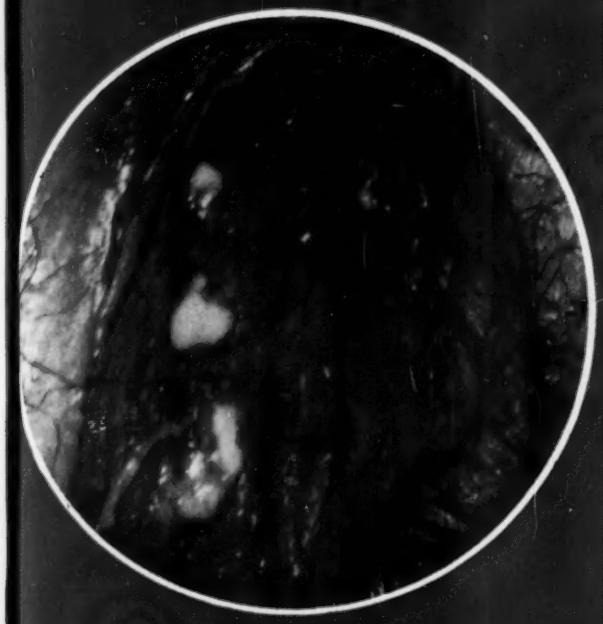
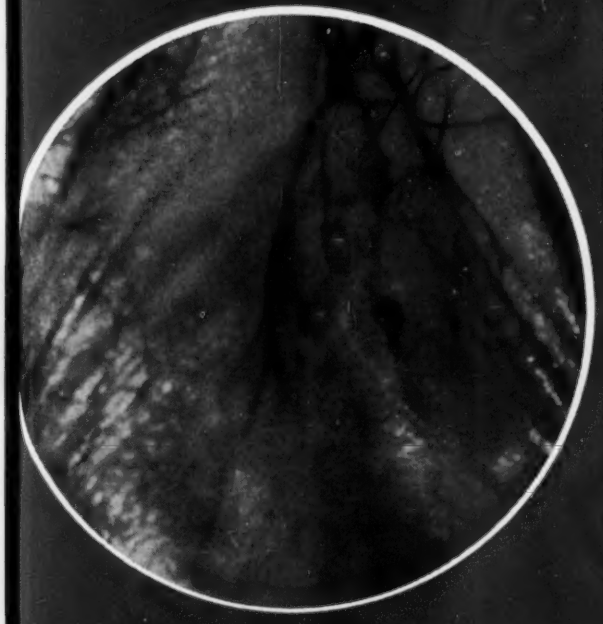
monilia responds to



oginal candidiasis (monilia) before treatment

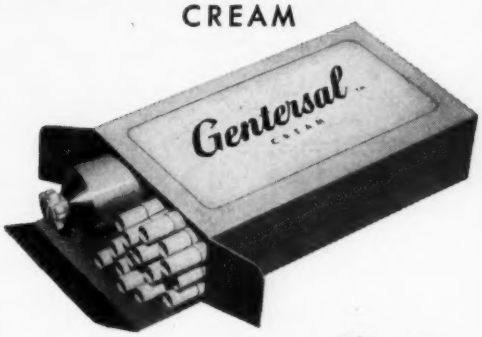


e patient after treatment with Gentersal cream

NEW effective therapy

Gentersal T. M.

CREAM



more effective

less irritating

less leakage (cream)

less staining

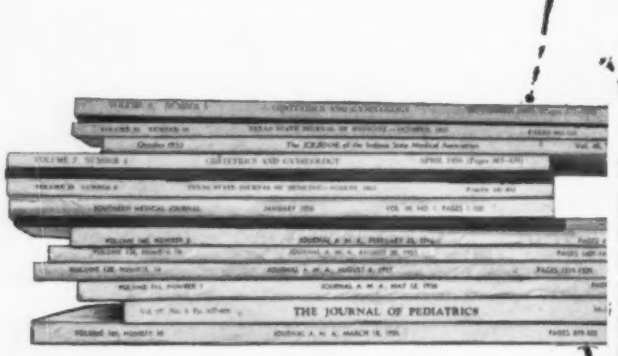
in large tubes with
15 disposable vaginal applicators.

Ortho

"The average female

is borderline

iron deficient..."[3]



IN MENSTRUAL

The bibliography specifies

1. Moore, C.V., and Dubach, R.: J.A.M.A. 162:197 (Sept. 15) 1956.
2. Holly, R.G.: Obstet. and Gynec. 2:124 (Aug.) 1953.
3. Ausman, D.C.: Journal-Lancet 76:290 (Oct.) 1956.

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ANEMIA . . .

Evidence shows that practically every menstruating female is in a state of precarious iron balance. Thus the iron deficiency state, due to even *normal* menstrual losses, is an extremely common occurrence.[1, 2]

Correction of this iron deficiency state results in real benefits to the tired, rundown female patient.

Strikingly superior clinical responses in menstrual anemia have been reported with RONCOVITE.[3] These results can be explained by the increased absorption and utilization of iron due to the improved bone marrow activity provided only by RONCOVITE.

Roncovite Tablets (*in menstrual anemia*):

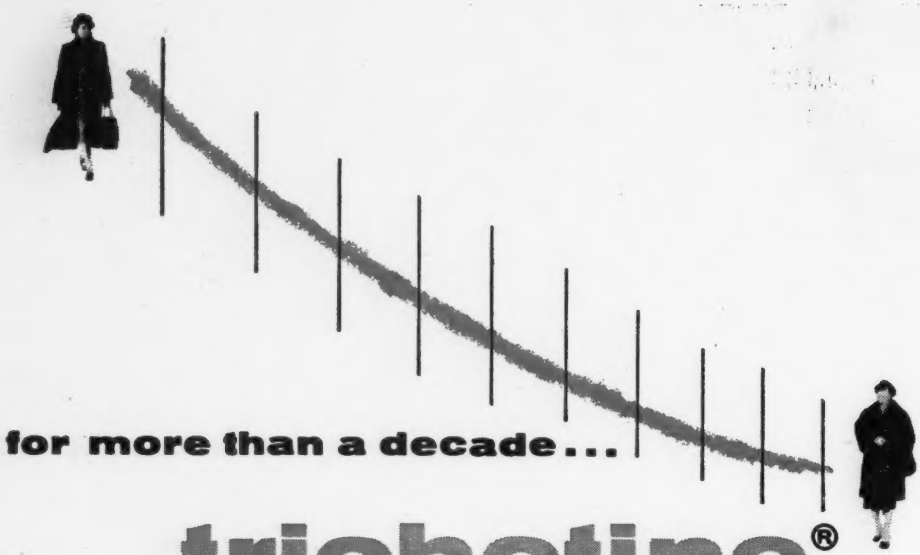
Maximum Adult Dosage: One tablet after each meal and at bedtime.

Bottles of 100 tablets.

Literature available to physicians on request.

Roncovite®

THE ORIGINAL, CLINICALLY PROVED COBALT-IRON PRODUCT



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...proved effective in vulvovaginal therapy

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Extensive clinical experience has proved its efficacy in trichomonas vaginalis vaginitis, subacute and chronic cervicitis, vulvovaginal moniliasis, non-specific leukorrhea, and pruritus vulvae.

Trichotine douches may be prescribed as often as indicated—excellent also for postmenstrual or postcoital hygiene. Concentrated solutions are useful for clean-up or swab treatments in office. Hot packs are often quickly effective in pruritus vulvae.

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AN AID TO EPITHELIZATION · AN AESTHETIC AND PSYCHOSOMATIC ADJUNCT

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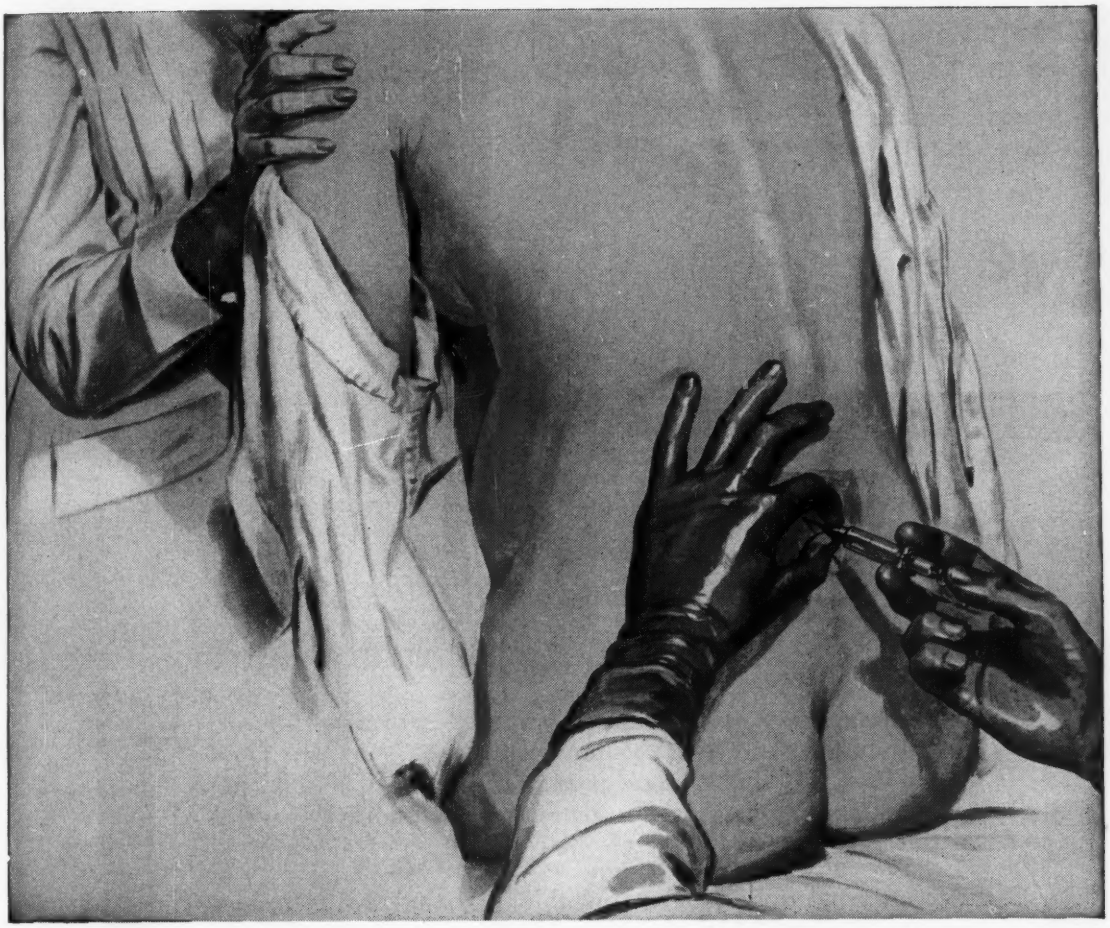
the fesler co., inc., 375 Fairfield Ave., Stamford, Conn.



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1. Causey, P. S., Reed, W. A., and Ford, J. L.: Arizona Med. *8*:27 (Dec.) 1951.

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Heavy Solution Nupercaine® hydrochloride (dibucaine hydrochloride with dextrose 5% CIBA).

I've Got a Secret

It's probably that he has a frog in his pocket... but his mother also has a secret... she's going to have a baby.

This intelligent modern mother has placed herself in the care of the physician in whom she has implicit faith. Now, the Doctor may, and probably does, prescribe a number of different prenatal supplements to his patients for various but valid reasons.

It is quite possible, indeed probable, that the physician may consider the use of a phosphorus-free, aluminum hydroxide containing product. Especially if it also provides organic iron, Vitamin B12 with intrinsic factor, plus the *important* vitamins in the *new* levels suggested for pregnant or lactating women. There are only a very *few* such quality formulas available for his choice.

One such formula with perhaps the easiest product name to remember on the national scene is Calcinatal® *(pronounced Calci' natal)* by Nion.

Patient acceptance of these easy-to-swallow tablets (not capsules) is quite understandable. Incidentally, one of your obstetrical problems, "control of Cramps" will be relegated to one of very minor incidence by use of the product. For more complete information, samples and brochure write to

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P.S. *We feel copy writers usually mention product names too often . . . . we mention ours but o*
It is so easy to remember and hard to forget. Say it once – try to forget it.

A DEMEROL® dosage form for every type of PAIN

DEMEROL HYDROCHLORIDE . . . *for prompt and prolonged control of severe pain*
AMPULS 1 cc. (50 mg.) and 2 cc. (100 mg.)
VIALS 30 cc. (50 mg./cc.)
TABLETS 50 mg. and 100 mg.
ELIXIR (50 mg. per teaspoonful)

A.P.C. WITH DEMEROL . . . *for less severe pain*
TABLETS containing aspirin 200 mg.
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DEMEROL WITH SCOPOLAMINE . . . *for preoperative medication, obstetric analgesia and amnesia*
Each 1 cc. contains 50 mg. Demerol HCl and
0.2 mg. (1/300 grain) scopolamine HBr.

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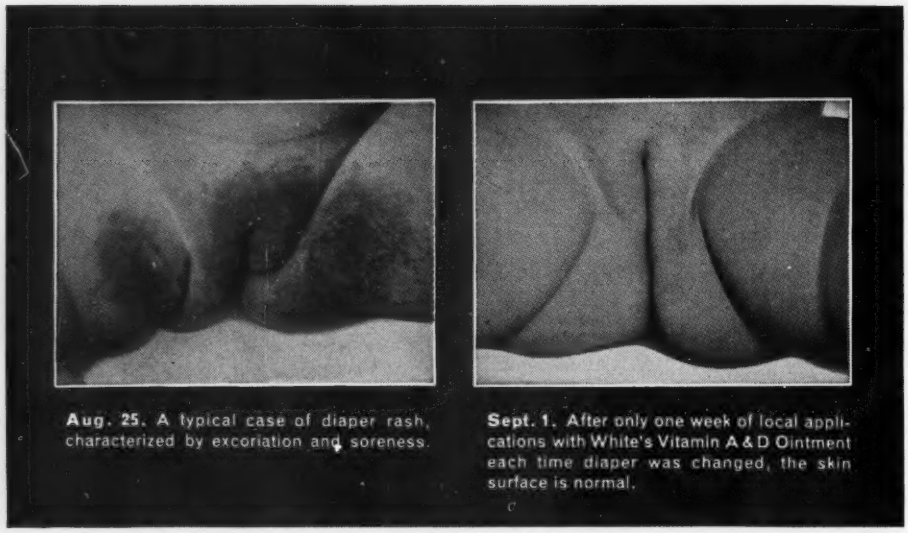

Aug. 25. A typical case of diaper rash, characterized by excoriation and soreness.

Sept. 1. After only one week of local applications with White's Vitamin A & D Ointment each time diaper was changed, the skin surface is normal.

it's becoming routine therapy

particularly in

prevention and treatment of diaper rash

and in many other common skin conditions: burns, cuts, sunburn, chafing, prickly heat, chapping, cracked nipples

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it's healing...soothing...protective.

Provides A & D vitamins in the same ratio as found in cod liver oil.

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KENILWORTH, N. J.

KEEP A TUBE OF THE NEW
ECONOMICAL, 4 OZ. SIZE
HANDY FOR EMERGENCIES
AND ROUTINE SKIN CARE

o simplify management of pregnancy constipation...

Colace

OCTYL SODIUM SULFOSUCCINATE, MEAD JOHNSON*

softens stools for easy passage

without laxative action · without adding bulk

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SUGGESTED ORAL DAILY DOSAGE

Adults and older children	50 to 200 mg.
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3 to 6 years	20 to 60 mg.
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NEW Colace Capsules 100 mg., bottles of 30, 60 and 250.

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Flight Plan for Anesthetic Objective

"... like a conscientious airman [the anesthesiologist] previously has filed a flight plan that, when carefully followed, leads to the objective. . . ."[1]

To relieve apprehension
To produce light sleep
To reduce the incidence of nausea and vomiting

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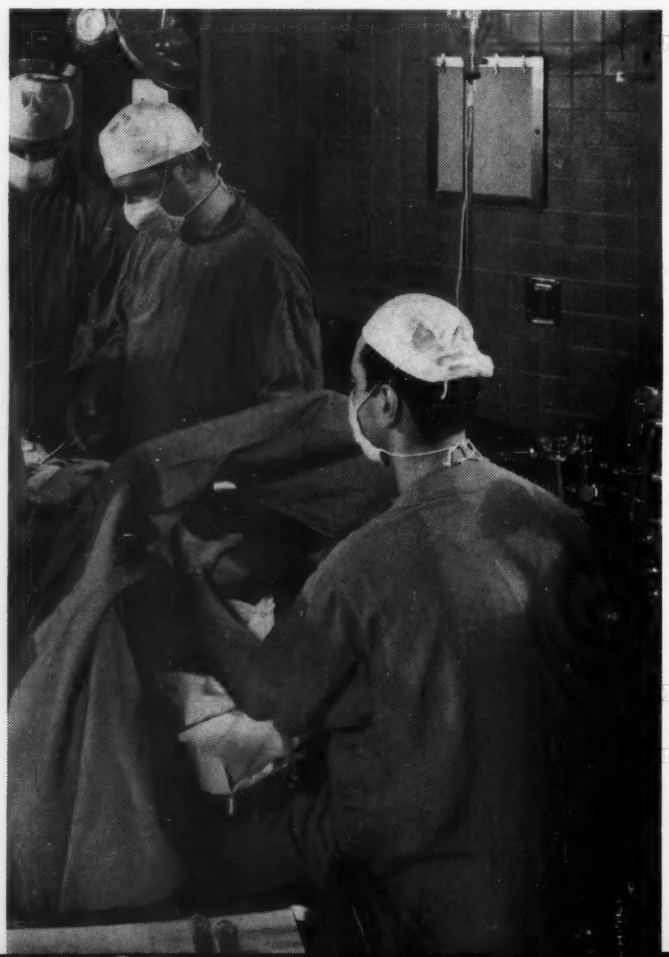
TABLETS INJECTION

PHENERGAN®

HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth



1. Lundy, J.S.: Chairman's address, Section on Anesthesiology, Annual Meeting, A.M.A., June 13, 1956; J.A.M.A. *162*:97 (Sept. 8) 1956.

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in over 3000 patients

"the most satisfactory drug . . . in the suppression of lactation."[1]

1. Eichner, E.; Goler, G. G.; Sharzer, S., and Horowitz, B.: Obst. & Gynec. 6:511, 1955.

TACE

(Chlorotrianisene)

the exclusive oral fat-stored estrogen[2]

2. Greenblatt, R. B., and Brown, N. H.: Am. J. Obst. & Gynec. 63:1361, 1952.

"The total absence of recurrent engorgement, the minimum amount of withdrawal bleeding, and the absence of almost all symptoms after the first few days has been noted by all using TACE."[1]

1. Eichner, E.; Goler, G. G.; Sharzer, S., and Horowitz, B.: Obst. & Gynec. 6:511, 1955.

"No product with which we are familiar equals TACE in effectiveness and safety."[3]

3. Bennet, E. T., and McCann, E. C.: J. Maine M. A. 45:225, 1954.

"Recurrence of symptoms and appearance of withdrawal bleeding are virtually eliminated, probably because of the storage of TACE in body fat and its gradual release after cessation of therapy."[4]

4. Nulsen, R. O.; Carmon, W. B., and Hendrick, H. O.: Am. J. Obst. & Gynec. 65:1048, 1953.

Dosage: 4 capsules daily, for seven days. *Also* . . . smoother relief of the menopause with less withdrawal bleeding...prolonged estrogenic effect.

TACE, the unique, fat-stored estrogen, released like a hormonal secretion for your menopause patient.

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Natalins-PF and Natalins are formulated for the busy, modern woman. Small in size, they're easy to take. Just 1 capsule t.i.d. supplies more than the increased requirements of essential vitamins and iron in pregnancy—plus a generous amount of calcium.

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Mead prenatal vitamin-mineral capsules—phosphorus-free

Contain calcium... no phosphorus

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Mead prenatal vitamin-mineral capsules

Contain both calcium and phosphorus

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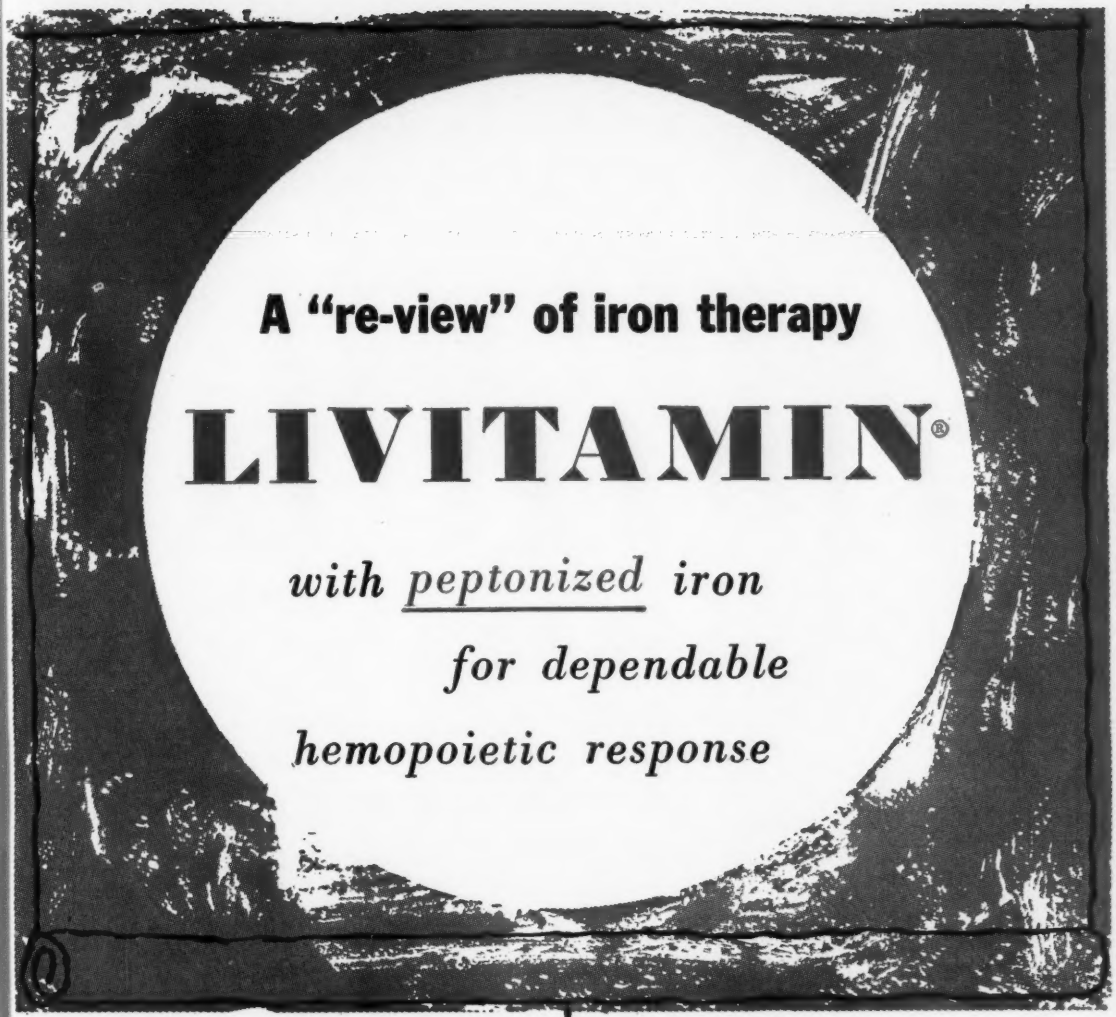

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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate. Read before the American Association for the Advancement of Science, Atlanta, Georgia, December, 1955

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Iron peptonized (Equiv. in elemental iron to 71 mg.)	0.42 Gm.
Manganese citrate, soluble	0.158 Gm.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
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Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

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diagnosis
without
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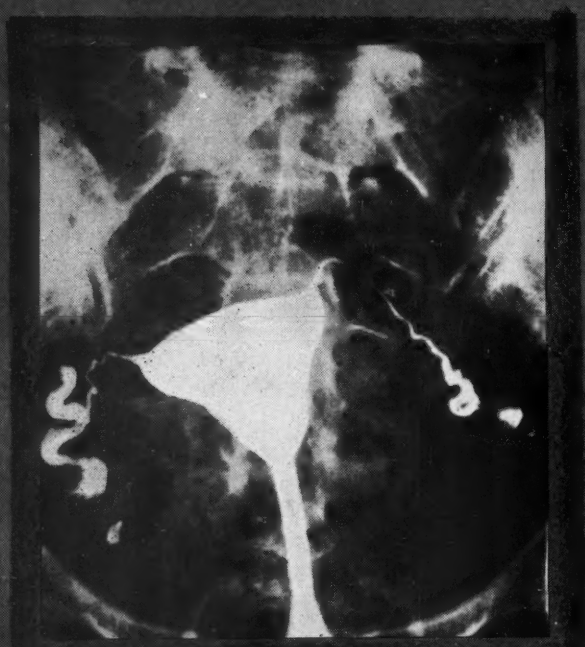

in hysterosalpingography
for detecting
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HOW TO GET BEST RESULTS AND ECONOMY IN APPLICATION

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1. Americaine provides relief in 2-3 minutes. Relief usually lasts 4-6 hours.
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3. Americaine is a simple, uncomplicated formula. This minimizes possibility of sensitivity. Not a single case of sensitivity was reported in 1866 published clinical cases. (Reprints on request.)

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Please enclose prescription blank when requesting

SMALL SIZE !
New 3 oz. dispenser is easy for patient to use.

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NOW, THREE SIZES: 11 oz. size for professional use and floor stock, 5.5 oz. and 3 oz. sizes for your prescriptions.

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Vitamin A	5,000 U.S.P. Units
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Thiamine mononitrate	3 mg.
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Folic acid	0.25 mg.
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Calcium, elemental	150 mg.
(as calcium carbonate 375 mg.)	
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(as ferrous sulfate exsiccated 33.6 mg.)	
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(as potassium iodide 0.2 mg.)	
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TERM-PAK

250 economical Engran tablets plus attractive, purse-size, tablet dispenser

- **maximal dosage convenience**
  just 1 small tablet daily
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  just 1 bottle holds nutritional support for the full term

for greatest patient cooperation in prenatal supplementation

Also available:
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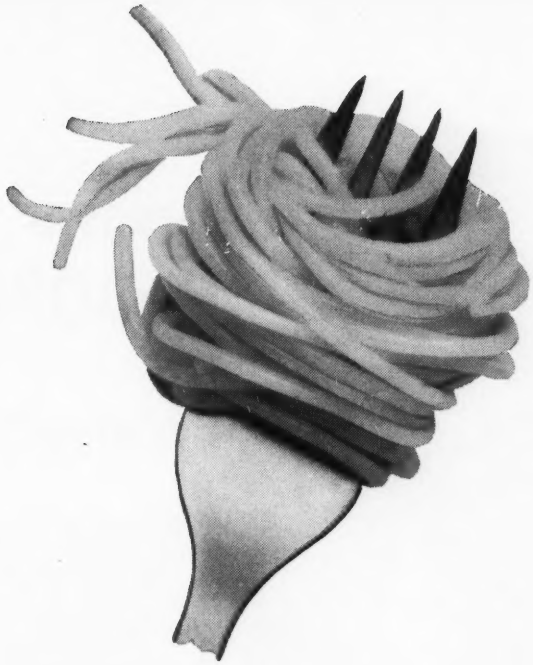
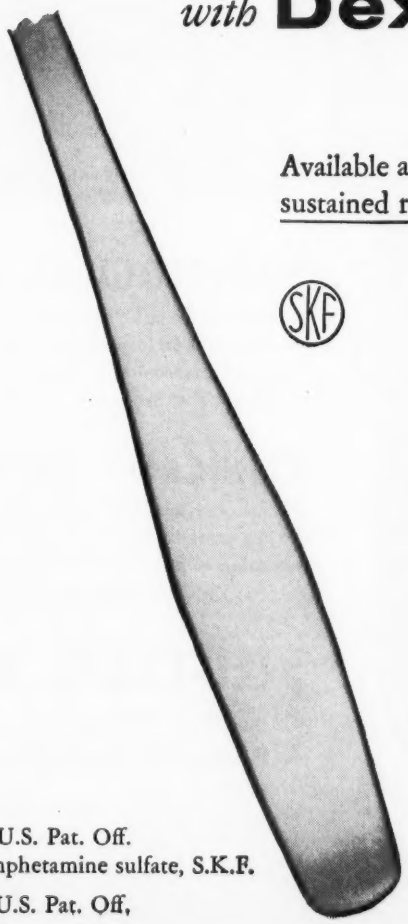


Overeating is a bad habit—
you can help your patients
to break it
with **Dexedrine***



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MEDOPAQUE-H for Hysterosalpingography

MEDOPAQUE-H is a sterile, completely absorbable, aqueous and viscous solution containing 35% Sodium Ortho-iodo-hippurate, 10% Sodium Iodide and a blend of polyethylene glycols.

$1.75 per 10cc. vial. In quantity as low as $1.50.

RADIOLOGICALLY SUPERIOR

Increased net iodine content (20%) in the improved Medopaque-H formula provides roentgenograms of superior contrast and diagnostic value. Altered anatomical status is clearly and sharply delineated.

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Thoroughly miscible, amply viscous, the new Medopaque-H formula is well tolerated. Completely absorbable polyethylene glycols now replace viscous CMC (carboxymethylcellulose).

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antibacterial
with
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A new antibacterial

with double-spectrum action

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Why is Gantrimycin so effective? Because it provides Gantrisin plus oleandomycin (a new antibiotic) which mutually reinforce each other; and there is a high degree of safety plus a pronounced effect on most pathogens resistant to other antibiotics.

The double-spectrum action of Gantrimycin is valuable against both gram-positive and gram-negative microorganisms.

Dosage: Adults—2 to 3 tablets, four times daily; should be increased to 4 or 5 tablets, four times daily, if necessary. Children over 30 lbs—1 or 2 tablets, four times daily. Children under 30 lbs—1 tablet, four times daily.

Each blue Gantrimycin tablet contains 333 mg Gantrisin and 75 mg oleandomycin.

Gantrisin®; Gantrimycin T.M.

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extra protection for every conception

Hesper-C Prenatal

with capillary-protective factors

a precaution in normal pregnancy *a necessity* in habitual abortion[1,2]

The problem of spontaneous abortion is not limited to habitual aborters. It is estimated that 10% to 20% of *all* pregnancies end in spontaneous abortion. Studies by Greenblatt,[1,3] Javert[4,5] and Dill[2] have revealed that integrity of the decidual vessels is a key to successful completion of pregnancy . . . and confirm that hesperidin complex and ascorbic acid, provided by Hesper-C Prenatal, restore and maintain capillary integrity.[6,7]

In several groups of habitual aborters, these researchers effected substantial fetal salvage—as high as 95% in one series[4]—when Hesper-C (hesperidin complex and ascorbic acid) was added to a regimen of prenatal supplementation and therapy.

Only Hesper-C Prenatal gives your patients the extra protection of hesperidin complex and ascorbic acid, plus the established prenatal vitamin-mineral supplementation, at a nominal increase in daily cost.

Hesper-C Prenatal is the only *complete* supplement for *all* your pregnant patients.

Each capsule contains:

Hesperidin Complex	100 mg.	Vitamin B_{12}	0.75 micrograms
Ascorbic Acid	100 mg.	Folic Acid	0.05 mg.
Vitamin A Acetate	1000 U.S.P. units	Pyridoxine Hydrochloride	1.67 mg.
Vitamin D_2	200 U.S.P. units	Calcium Pantothenate	1.0 mg.
Thiamine Mononitrate	1.25 mg.	Ferrous Gluconate (2.5 mg. iron)	21.6 mg.
Riboflavin	0.75 mg.	Calcium Carbonate (83.3 mg. calcium)	208.25 mg.
Nicotinamide	5.0 mg.	Copper Sulfate (0.5 mg. copper)	2.0 mg.
		Potassium Iodide (0.05 mg. iodine)	0.065 mg.

In bottles of 100 and 500 capsules.

Recommended daily dose: Two capsules t.i.d.
Providing the daily requirements or more of vitamins and iron during pregnancy as recommended by the National Research Council.

References: 1. Greenblatt, R. B.: Obst. & Gynec. *2*:530, 1953. 2. Dill, L. V.: M. Ann. District of Columbia *23*:667, 1954. 3. Greenblatt, R. B.: Ann. New York Acad. Sc. *61*:713, 1955. 4. Javert, C. T.: Obst. & Gynec. *3*:420, 1954. 5. Javert, C. T.: Ann. New York Acad. Sc. *61*:700, 1955. 6. Barishaw, S. B.: Exp. Med. & Surg. *7*:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: Am. J. Digest. Dis. *17*:92, 1950.

Products of Original Research

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Philadelphia 44, Pa.

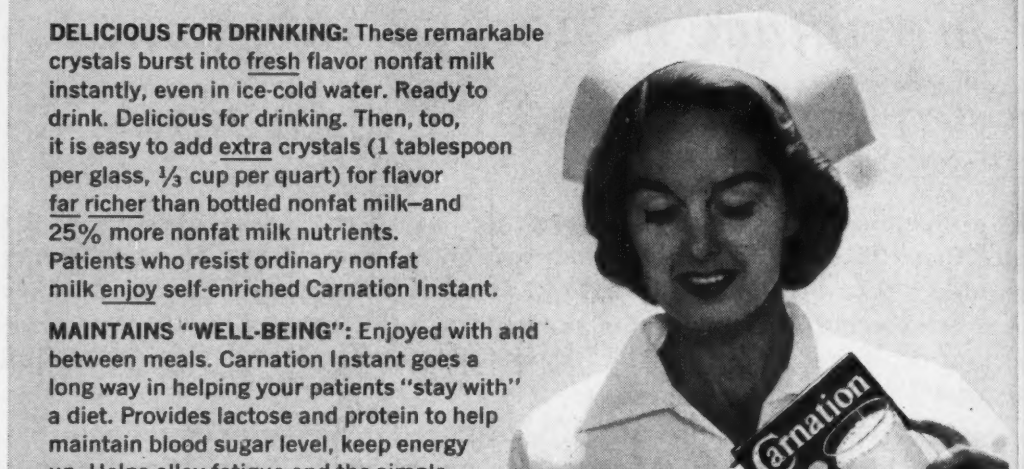
"DOCTOR, have you tried new Carnation Instant?"

YOU'LL DISCOVER WHY THIS EXCLUSIVE CRYSTAL FORM OF NONFAT MILK HELPS YOUR PATIENTS "STAY WITH" A DIET...IT TASTES SO GOOD!

DELICIOUS FOR DRINKING: These remarkable crystals burst into fresh flavor nonfat milk instantly, even in ice-cold water. Ready to drink. Delicious for drinking. Then, too, it is easy to add extra crystals (1 tablespoon per glass, ⅓ cup per quart) for flavor far richer than bottled nonfat milk–and 25% more nonfat milk nutrients. Patients who resist ordinary nonfat milk enjoy self-enriched Carnation Instant.

MAINTAINS "WELL-BEING": Enjoyed with and between meals. Carnation Instant goes a long way in helping your patients "stay with" a diet. Provides lactose and protein to help maintain blood sugar level, keep energy up. Helps allay fatigue and the simple hunger pangs that make it hard to resist forbidden snacks.

WHY NOT try new Carnation Instant yourself? A fine, protective "boost" for the busy physician. Ready instantly, fits into your most crowded professional day.



TODAY'S COLLEGE GRADUATES HAVE BIGGER FAMILIES—PLANNED BIG

EVEN COLLEGE GRADUATES, traditionally the low-birthrate group, are having big families today. Planning them bigger. A survey just completed among 29,494 graduates of 178 colleges shows that the men of the class of '45 have families *averaging* 70% larger than those of the class of '36 in the ten years after graduation.[1]

Want big, but spaced, families—When these wives come to you for contraceptive advice so that they can *space* their large families, they want to be sure that the recommended method *really* gives them protection. You can give them this assurance with diaphragm and jelly—*the preferred technique for women of high parity.* These patients may not be as well protected by use of jelly alone, a method that seems better suited to low-parity women. In urban population groups using the diaphragm-jelly method, unplanned pregnancy occurred only "once in ten to 15 years."[2]

Security plus comfort—RAMSES® Diaphragm and Jelly assure comfort as well as peace of mind for your patient. The cushioned, flexible rim of the RAMSES Diaphragm permits complete freedom of movement, causes no irritation. RAMSES Jelly,* a "10-hour jelly," quickly immobilizes sperm and occludes *for a full ten hours.*

When patients learn that for more than 30 years physicians have relied on RAMSES Diaphragms and Jelly to help plan families—big families—they will feel confident of receiving sound advice. RAMSES "TUK-A-WAY"® Kit #701 (diaphragm, introducer and jelly in a neat zippered bag), RAMSES Diaphragms 50-95 millimeters in size, RAMSES Jelly in 3 and 5 oz. tubes.

1. College Study Report: Population Bulletin *11*:45 (June) 1955. **2.** Tietze, C., in Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Co., 1950, pp. 55-57.

RAMSES and "TUK-A-WAY" are registered trade-marks of Julius Schmid, Inc.

*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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a unique new compound, ferrous calcium citrate, with tricalcium citrate

- iron and calcium in one molecule
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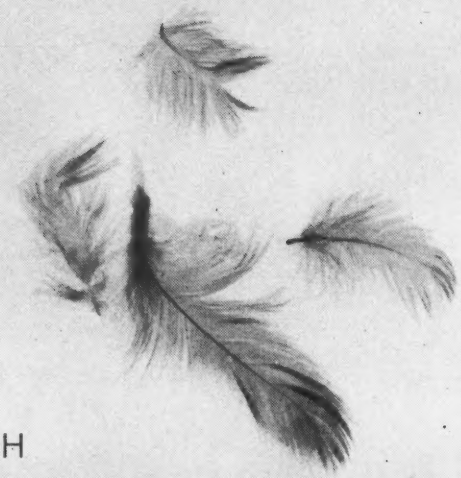
TABLETS

• a complete phosphorus-free prenatal supplement

3 tablets daily provide:

Ferrous calcium citrate with tricalcium citrate	1500 mg.
Calcium	255 mg.
Iron	75 mg.
Vitamin A	6000 U.S.P. units
Vitamin D	1200 U.S.P. units
Thiamine hydrochloride (B_1)	3 mg.
Riboflavin (B_2)	3 mg.
Niacinamide	30 mg.
Ascorbic acid (C)	100 mg.
Pyridoxine hydrochloride (B_6)	3 mg.
Calcium pantothenate	6 mg.
Vitamin B_{12}	3 mcg.
Folic acid	1 mg.

Ortho



SURGEONS WITH

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CHOOSE FINER SIZES OF D&G GUT

"Gentleness in handling fragile tissues must be mastered, and the feather touch is essential."

Potts, W. J.: J. A. M. A. 157:627 (Feb. 19) 1955, p. 629.

SURGEONS APPRECIATE the smooth flexible "hand" of D & G gut. They sense the extra knot security offered by D & G's special matte finish.

The rapid trend to the regular use of 000, 4-0 and 5-0 gut in the past five years has brought increased recognition of the values of D & G gut. Special processing assures the most strength with the least gut—unlike ordinary gut which is ground to size with some loss of flexibility and tensile strength.

D & G gut — other gut

The finer sizes of D & G plain, mild chromic and medium chromic gut are, and have been, the acknowledged world-wide standard for gastrointestinal and eye surgery for over twenty years.

When you want to approximate mucous membranes... repair tissues of the neck... ligate small blood vessels . . . or whenever you want to use your "feather touch," check with your O R Supervisor to be sure you have the advantages of finer sizes of D & G gut.

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"...nauseated and vomiting every day, practically the whole day, from the beginning of this pregnancy..."

After 'Compazine' 5 mg. q.i.d., this severe case[1] of nausea and vomiting of pregnancy showed " . . . almost immediate response."

In fact, the physician reports, "She hasn't had any nausea or vomiting since then and she has not had the drug for three weeks."

'Compazine' is a potent new antiemetic that has shown 86% favorable results in the treatment of nausea and vomiting of pregnancy. In over 12,000 patients, treated with 'Compazine' before introduction, side effects were infrequent, minimal and transitory.

Compazine★

a potent new antiemetic for everyday practice

Smith, Kline & French Laboratories, Philadelphia

1. Personal communication to S.K.F.

★Trademark for proclorperazine, S.K.F.

Estrogen-androgen therapy effectively prevents postpartum breast engorgement

Satisfactory results were obtained in over 96 per cent of cases in a series of 267 patients who received estrogen and androgen as combined in "Premarin" with Methyltestosterone. Therapy was started as soon as possible after delivery. No untoward side effects were noted. In addition, the absence of mental depression in the puerperium was considered of notable importance.*

*Fiskio, P. W.: GP *11*:70 (May) 1955.

"PREMARIN"® with METHYLTESTOSTERONE

for combined estrogen-androgen therapy

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recommended for routine prophylaxis in ALL pregnancies . .

96 per cent live delivery with **des**PLEX in one series of 1200 patients[4]— — bigger and stronger babies, too.[cf. 1]

No gastric or other side effects with **des**PLEX — in either high or low dosage[3,4,5]

(Each **des**PLEX tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating *to assure prompt help in emergencies.* **des**PLEX tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous trial supply of **des**PLEX, write to:
Medical Director

REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J.: South. M. J. 45:1166, 1952.
4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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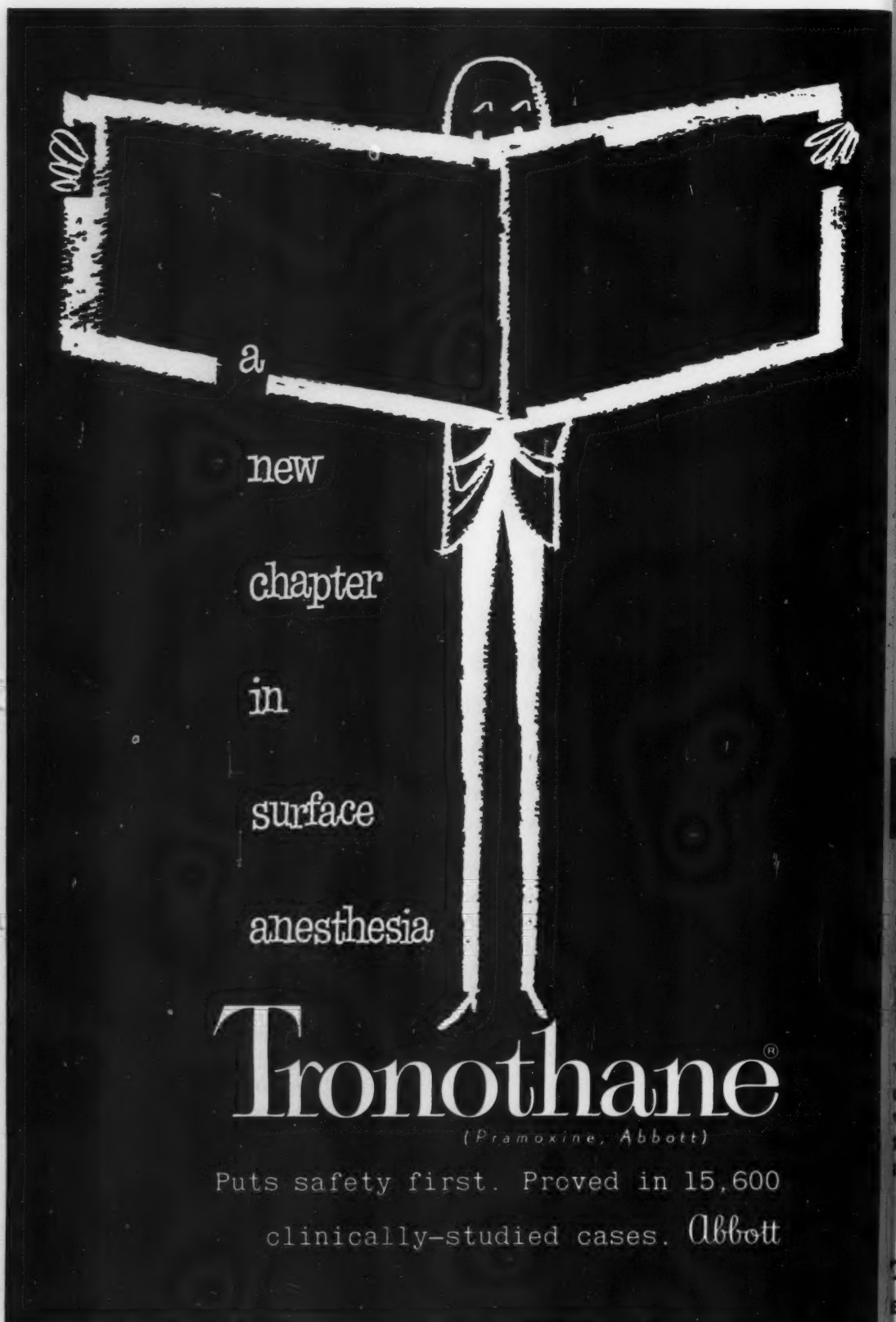
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Puts safety first. Proved in 15,600
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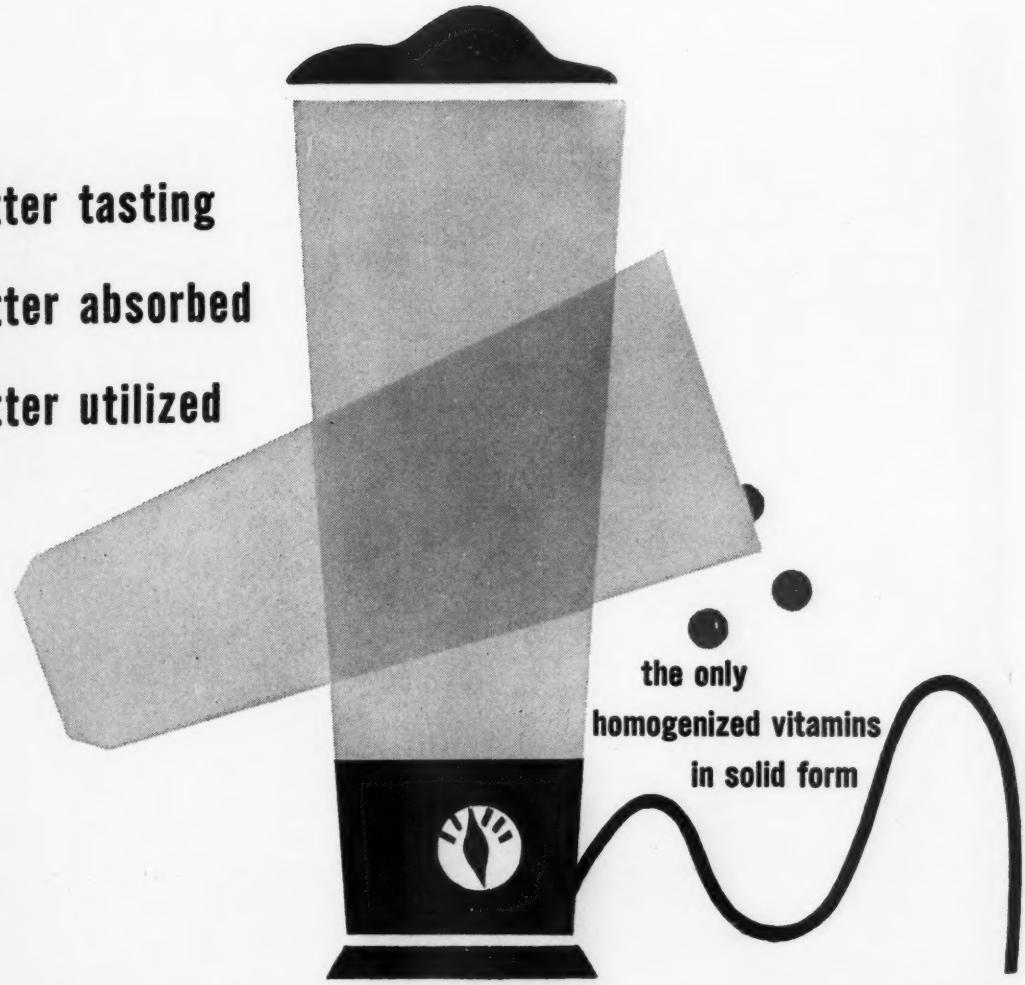

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Homogenization presents both oil and water soluble vitamins in microscopic particles. This permits greater dispersion of the vitamins—thus better absorption and utilization. And the flavorful base assures patient acceptance.

*U.S. Pat. 2676136. Other Pat. Pending

Advantages—

Better absorption, better utilization

Excess vitamin dosage unnecessary

Pleasant, candy-like flavor

No regurgitation, no "fishy burp"

May be chewed, swallowed or dissolved in the mouth

Three formulas:

Prenatal Pediatric Therapeutic

Send for samples of Homagenets. Taste them, and compare.

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Naturally she'll appreciate efficacy with elegance

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for natural acceptance of your prescribed contraceptive regimen • fulfills your patient's natural wish that her possessions reflect her femininity. Each Lanteen Exquiset contains: 3 oz. tube of Lanteen spermicidal jelly, soothing, cleanly scented; easy-to-insert, molded, flat spring diaphragm; *Easy-Clean* applicator; universal inserter — all fitted into a stylish, soft plastic purse.

Lanteen jelly contains ricinoleic acid 0.50%, hexylresorcinol 0.10%, chlorothymol 0.0077%, sodium benzoate and glycerin in tragacanth base. Lanteen jelly and flat-spring diaphragm sets are distributed by George A. Breon & Company, 1450 Broadway, New York 18, N.Y. (In Canada: E. & A. Martin Research Ltd., 20 Ripley Ave., Toronto, Canada.) Manufactured by Esta Medical Laboratories, Inc., Chicago 38, Ill.

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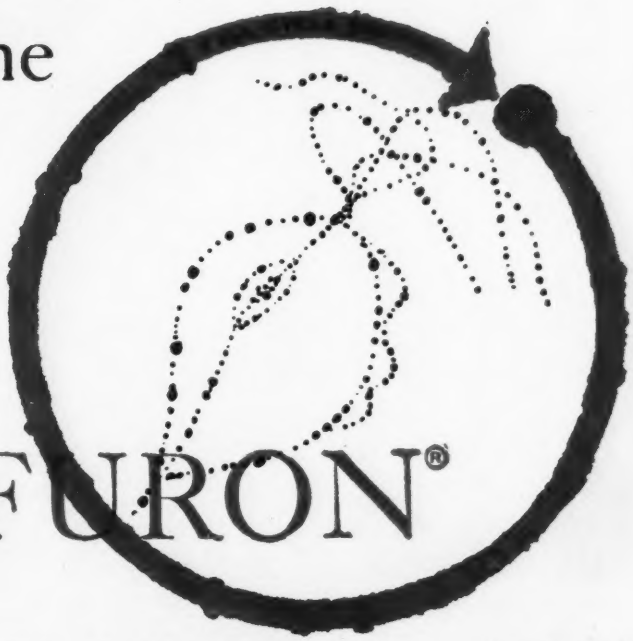
Even stubborn trichomoniasis yields... because Tricofuron is effective during menstruation, the critical time for therapy.



TRICOFURON®

Recurrences of trichomoniasis "are most likely to follow the menstrual period."[1]

"Over and over again today patients are seen with what is said to be an intractable, treatment-resistant Trichomonas infestation, but history-taking often reveals that such patients have never had treatment prescribed during any menstrual period."[2]

Menstrual blood in the vagina "forms an excellent medium for the rapid multiplication of T. vaginalis"[3] and "lowers the acidity of the vagina and hence there is a tendency to recrudescence [of trichomoniasis] at that time."[4]

Tricofuron is powerfully trichomonacidal "even in the presence of vaginal debris and menstrual blood."[3]

For 44 of 48 patients: lasting cure was obtained with a single course of Tricofuron therapy.[3]

Vaginal Suppositories—for home use—each morning and night through one cycle, including the important menstrual days. Contain 0.25% Furoxone® (brand of furazolidone) in a water-miscible base. Box of 12, each sealed in green foil.

Vaginal Powder—for office use—applied by the physician at least once a week, except during menstruation. Contains 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

References: 1. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations and Discharges, New York, The Blakiston Company, Inc., 1953, p. 235. 2. Overstreet, E. W.: Arizona M. 10:383, 1953. 3. Schwartz, J.: Obst. Gyn., N. Y. 7:312, 1956. 4. Crossen, R. J.: Diseases of Women, St. Louis, The C. V. Mosby Company, 1953, p. 292.

EATON LABORATORIES *NORWICH, NEW YORK*

Nitrofurans—a new class of antimicrobials—neither antibiotics nor sulfonamides

TREAT HER MORNING SICKNESS...THE NIGHT BEF

NEW

Bendecti

...In 200 cases, effective in all but one.[1]

Long-acting **Bendectin,** new anti-emetic, unusually effective in prevention of nausea and vomiting of pregnancy. **Bendectin** gives your patient the benefit of three distinct and complementary modes of action:

1. **antispasmodic** — relaxes G.I. smooth-muscle spasm
2. **antinauseant** — centrally effective
3. **nutritional supplementation** — to overcome possible pyridoxine deficiency of pregnancy

...Relieves morning sickness "before it starts"

Other advantages include:

4. simple, convenient bedtime dosage
5. low cost to patient

Bendectin contains in each specially coated tablet:

Bentyl (dicyclomine) Hydrochloride . 10 mg.
Decapryn (doxylamine) Succinate . . . 10 mg.
Pyridoxine Hydrochloride . . . . . 10 mg.

USUAL DOSAGE: 2 tablets at bedtime.

SUPPLIED: Bottles of 100 tablets.

1. Nulsen, R. O.: Ohio State M.J. (In press)

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TRADEMARKS: 'BENDECTIN', 'BENTYL', 'DECAPRYN'

lifesaving technique for the unborn *includes* high citrus intake

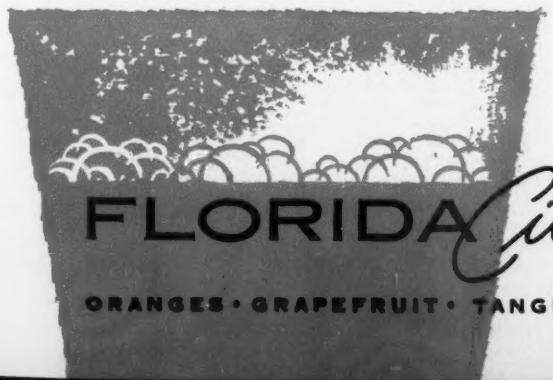
Abortion-prone mothers deliver live babies in nearly 9 out of 10 pregnancies

Reporting on 134 pregnancies in 100 habitual abortion patients, Javert* describes a management program that resulted in live deliveries in all but 16 pregnancies. The previous 95.2 per cent rate of spontaneous abortions was reduced to 11.9 per cent by his comprehensive regimen which includes a high citrus intake (supplying up to 350 mg. of vitamin C daily), supplemented by 150 mg. of ascorbic acid and 5 mg. of vitamin K daily. Javert believes these antihemorrhagic vitamins "serve as a 'never-leak' . . . keeping physiologic decidual hemorrhage from becoming pathologic."

AVERAGE CITRUS INTAKE TO SUPPLY 350 MG. VITAMIN C DAILY

28 oz. orange or grapefruit juice	**or**	1 grapefruit 2 oranges 2 tangerines	**or**	½ grapefruit 1 orange 16 oz. orange juice

Florida Citrus Commission, *Lakeland, Florida*



*Javert, C. T.: Obst. & Gynec. 3:420, 1954; *Cf.* Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

Mol-Iron

MOLYBDENIZED FERROUS SULFATE

"We have never had other iron salt so efficacious in pregnant patients, —well tolerated even by iron-intolerant patients"[2,3]

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1. Dieckmann, W. J., and Priddle, H. D., Anemia of Pregnancy Treated with Molybdenum-Iron Complex, Am. J. Obst. & Gynec. 57:541, (March) 1949.
2. Neary, E. R., Am. J. Med. Sc. 212:76 (July) 1946.
3. Kelly, H. T.: Pennsylvania M. J. 51:999 (June) 1948.

the only

prenatal supplement

with **Mol-Iron**

Gestatabs® tablets

"just 2 for 2"

—for real patient convenience

only 2 tablets a day

Available in bottles of 60 tablets

PHOSPHORUS-FREE CALCIUM
to minimize the likelihood of leg cramps

VITAMIN K
to bolster prothrombin levels

ESSENTIAL VITAMINS
to maintain normal pregnancy

and when iron is the dominant need...

Mol-Iron with calcium and vitamin D

Available in bottles of 60 tablets

for the modern woman...a modern prenatal supplement

Today's pregnant woman is more fortunate than her sister of yesteryear . . . she looks better, feels better and enjoys greater freedom during her pregnancy. She is free, too, from such traditional prenatal distress as leg cramps, irritability and mild edema when a *modern* prenatal supplement is prescribed.

Usable calcium—Recent evidence points to a new rationale of prenatal nutrition. ". . . it is apparent that dicalcium phosphate, so widely used as a dietary supplement in pregnancy, is undesirable."* Calcisalin, for routine prenatal supplementation, provides calcium in the *usable* form of the lactate salt, rather than phosphate.

The complete prenatal supplement – Calcisalin also provides reactive aluminum hydroxide gel (to absorb excess dietary phosphorus) and the minimum daily vitamin and iron allowances for pregnancy as recommended by the National Research Council.

Thus the risk of inadvertently raising the phosphorus level to the point where it interferes with calcium absorption is avoided with Calcisalin.

Dosage: Two tablets three times daily after meals. *Available:* Bottles of 100 tablets and 8-oz. reusable nursing bottles containing 300 tablets.

*Page, E. W., and Page, E. P.: Obstet. & Gynec. *1*:94 (Jan.) 1953.

Calcisalin®

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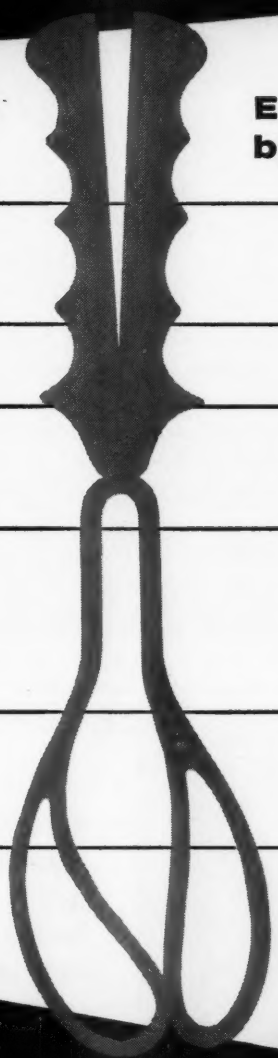
does WHAT YOU WANT A GOOD TOPICAL ANESTHETIC TO DO

doesn't DO WHAT YOU'RE AFRAID SUCH A POTENT AGENT MIGHT DO



Criteria of the ideal topical anesthetic[1]	Evaluation of DYCLONE by these criteria
RAPID EFFECT	Dyclone is a rapid acting local anesthetic.[1-4]
HIGH POTENCY	Dyclone has a high degree of potency.[1-3]
SAFETY	Large areas can be treated without danger; safe even if complete absorption is assumed.[1]
LOW SENSITIZING POTENTIAL	In more than 5,000 reported cases sensitization to Dyclone was less than 0.1%. No instance of cross sensitization with other topical anesthetics was found.[5]
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references: 1. Shelmire, B.; Gastineau, F. M., and Shields, T. L.: Arch. Dermat. 71: 728, 1955. 2. Hungerford, L. N.: Bull. Mason Clin. 9: 105, 1955. 3. Arora, R. B., et al.: E.E.N.T. Monthly 34: 593, 1955. 4. Morginson, W. J., et al.: Postgrad. Med. 19: 605, 1956. 5. Data from Pitman-Moore Research Files.

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the NEW topical anesthetic with bactericidal properties

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Write for literature and samples.

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added certainty in treatment of respiratory infections

new multi-spectrum synergistically strengthened antibiotic formulation

SIGMAMYCIN adds certainty in antibiotic therapy, particularly for the 90% of patients treated at home or in the office where sensitivity testing may not be practical, and provides: a new maximum in therapeutic effectiveness, a new maximum in protection against resistance, a new maximum in safety and toleration.

Supply: Capsules, 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.). Bottles of 16 and 100.

. . . and for a new maximum in palatability

New mint-flavored Sigmamycin for Oral Suspension, 1.5 Gm. in 2 oz. bottle; each 5 cc. teaspoonful contains 125 mg. (oleandomycin 42 mg., tetracycline 83 mg.).

*Trademark

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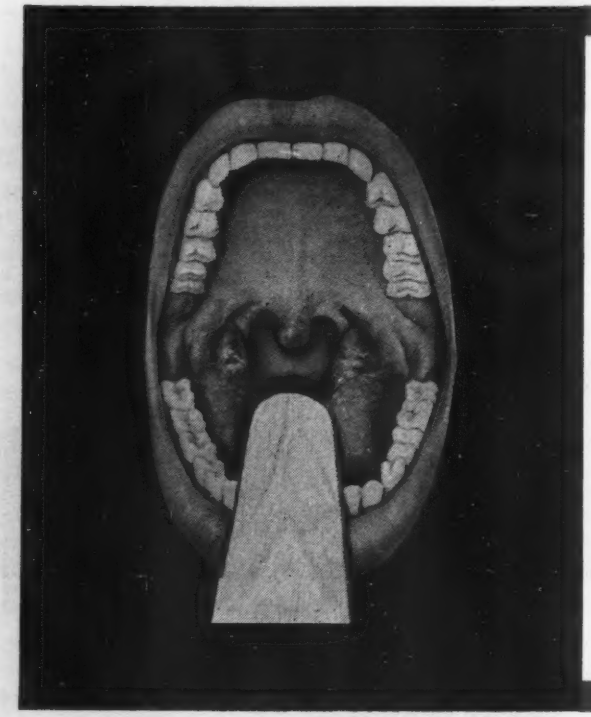
World leader in antibiotic development and production



"...effective...in the treatment of a variety of infections seen regularly by the practicing clinician..." including pharyngitis, bronchitis and other respiratory infections

and "... often useful in the treatment of infections due to staphylococci resistant to one or several of the regularly used antibiotics"

"side effects . . . [are] notable by their absence"[1]

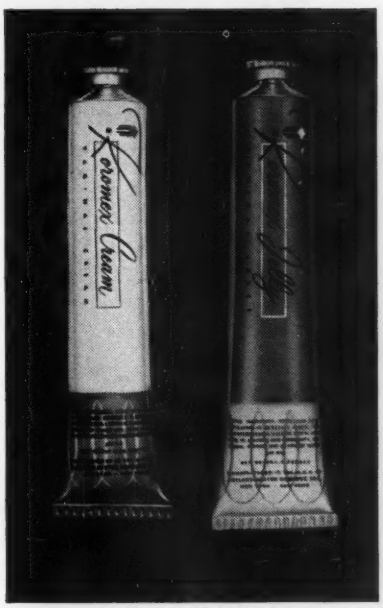
1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51.

This is a doctor. We know the toils of his education dedicate him to his daily work. We also know that his work is varied, complex, and always demands a broad personal and infinitely professional approach. His may be a rewarding chore... but it's a most trying one. Above all, his responsibility is the restoration and preservation of the health of those who seek his help.

It is for these men that we devote intensive research and study techniques to provide for them the finest conception control products. History indicates... if product demand is an index... that ours assure consistently more effective results*. We're pleased that doctors of America have proven this.

That's why they rely on and recommend... *Koromex*

*Factual literature sent on request.



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"...Dramamine nevertheless proved more effective than other methods hitherto employed in the concededly difficult management of nausea and vomiting of pregnancy."

Cartwright, E. W.: Dramamine in Nausea and Vomiting of Pregnancy, West. J. Surg. *59*:216 (May) 1951.

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In deference to her daintiness...

- Massengill Powder is buffered to *maintain** an acid condition in the vaginal mucosa. It is more effective than vinegar and simple acid douches.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill powder®

when recommending a vaginal douche

indications:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

*In a recent clinical report, ambulatory patients —with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours.

*Arnot, P.H.: West. J. Surg., Obs., and Gyn. 62:85

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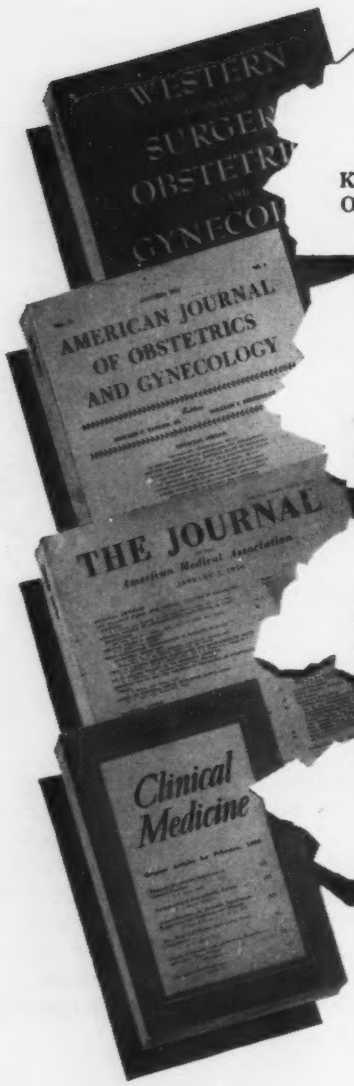

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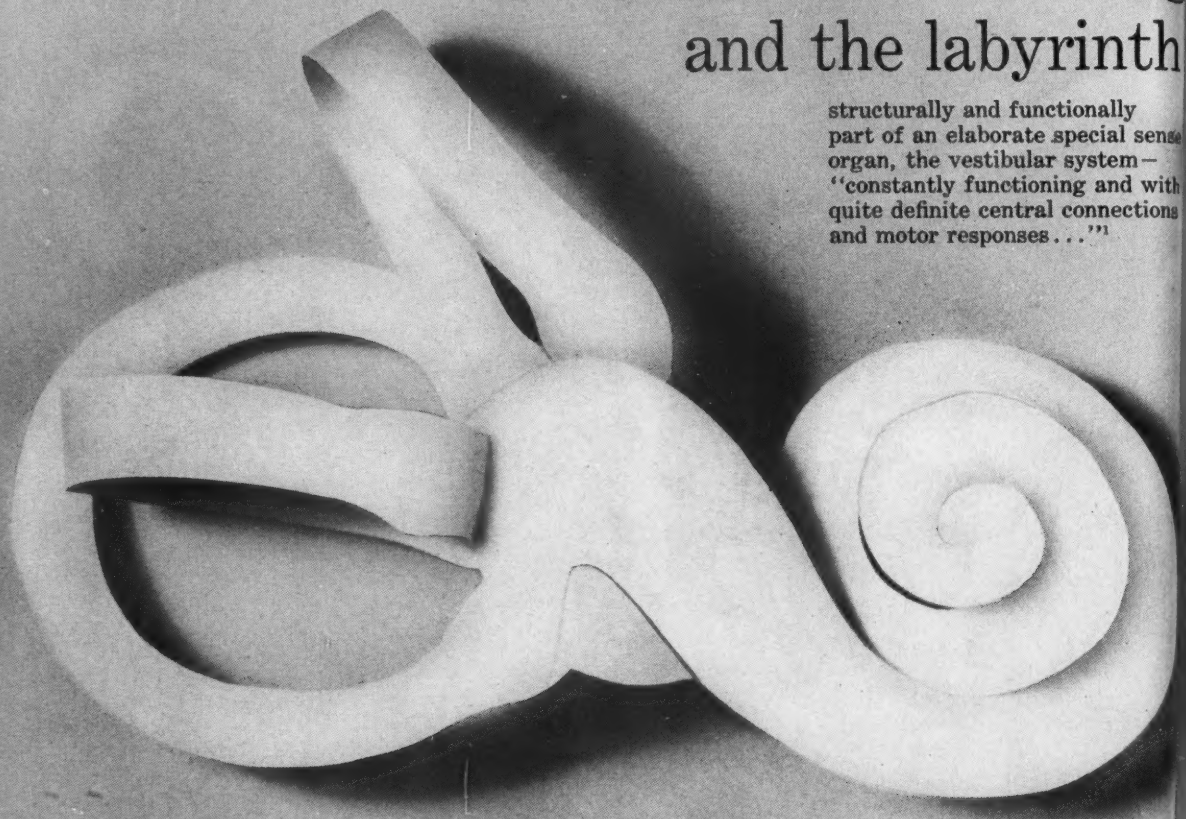

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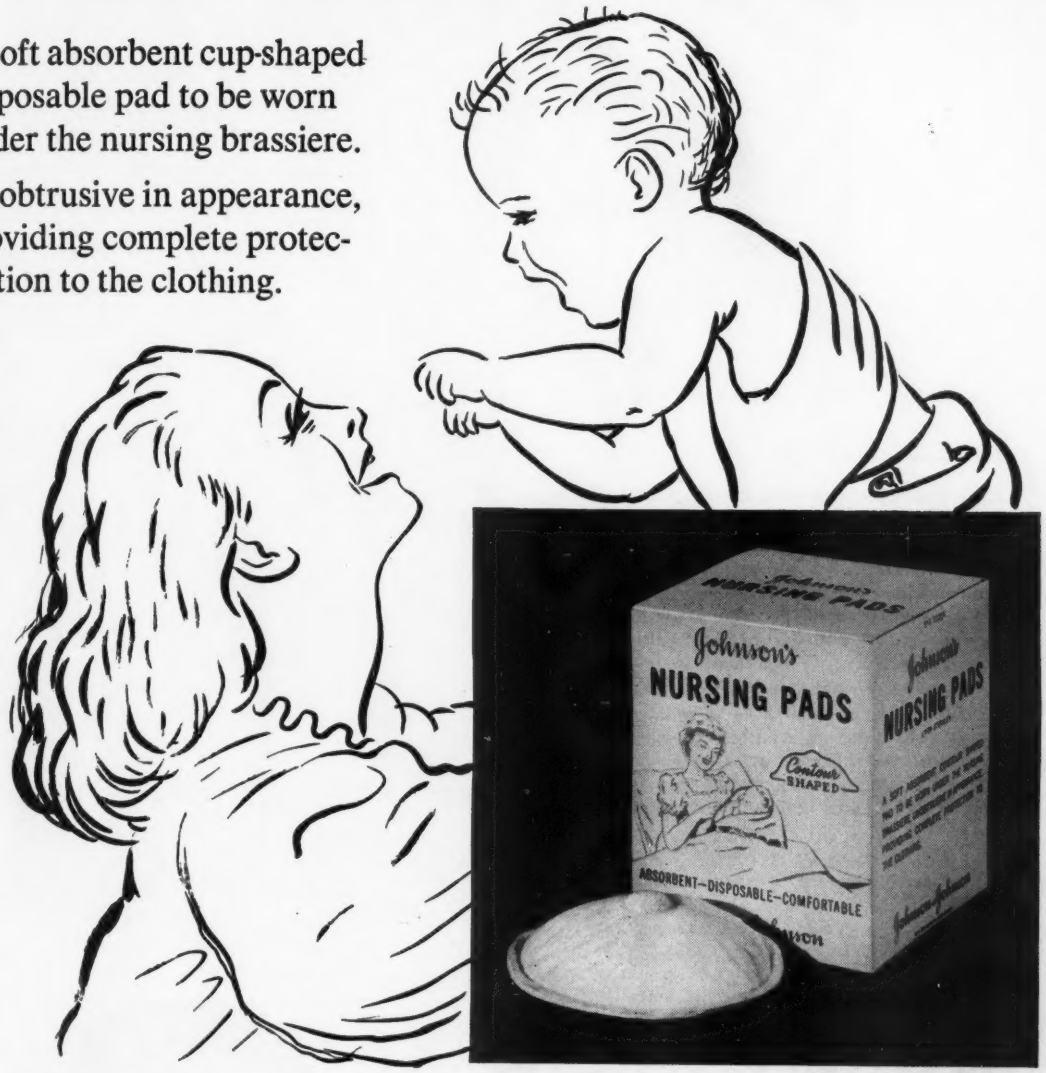

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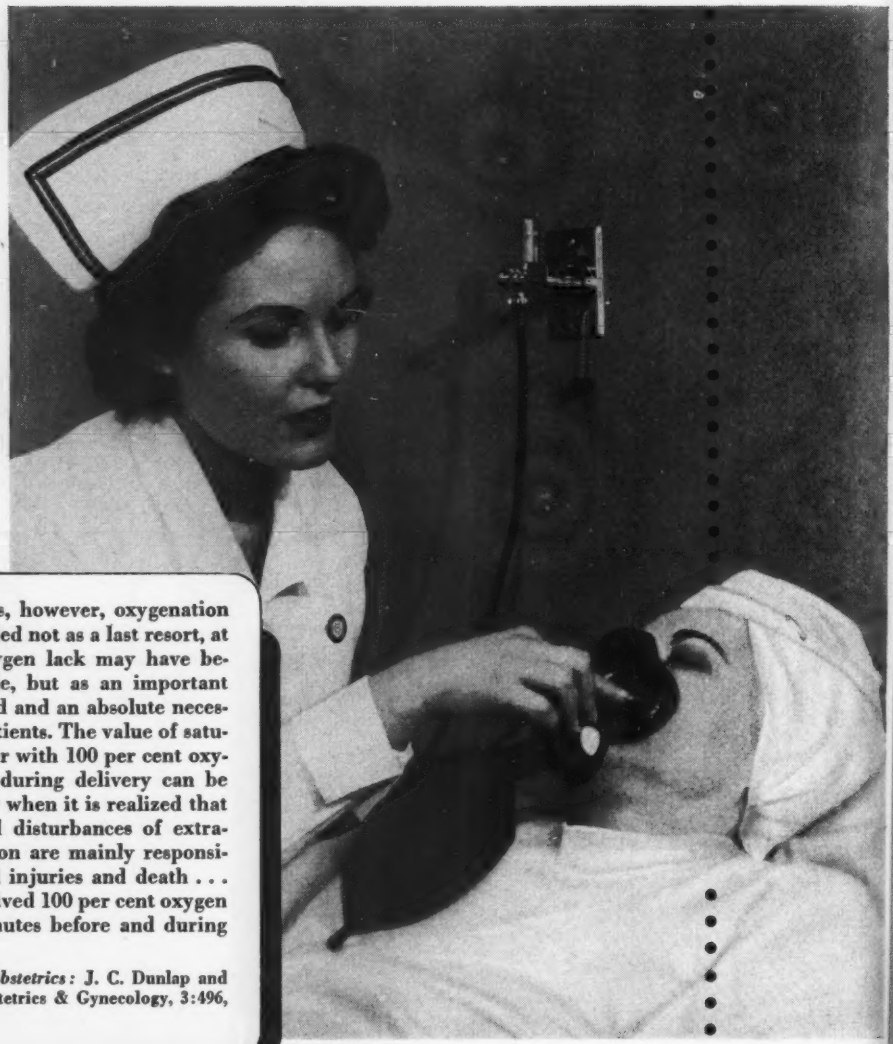

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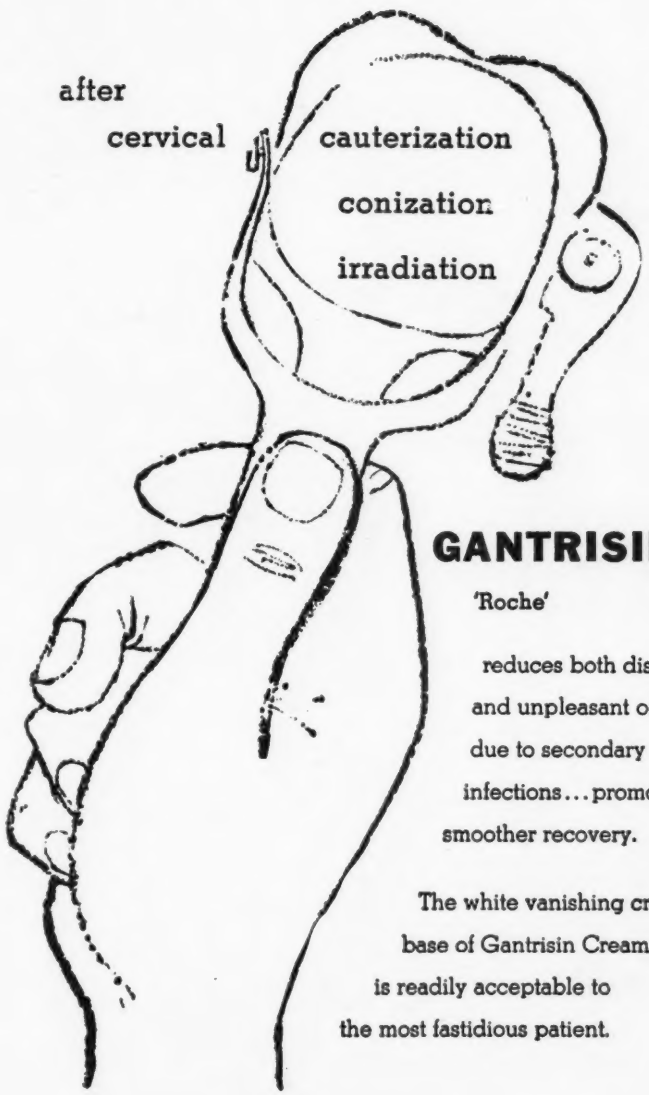

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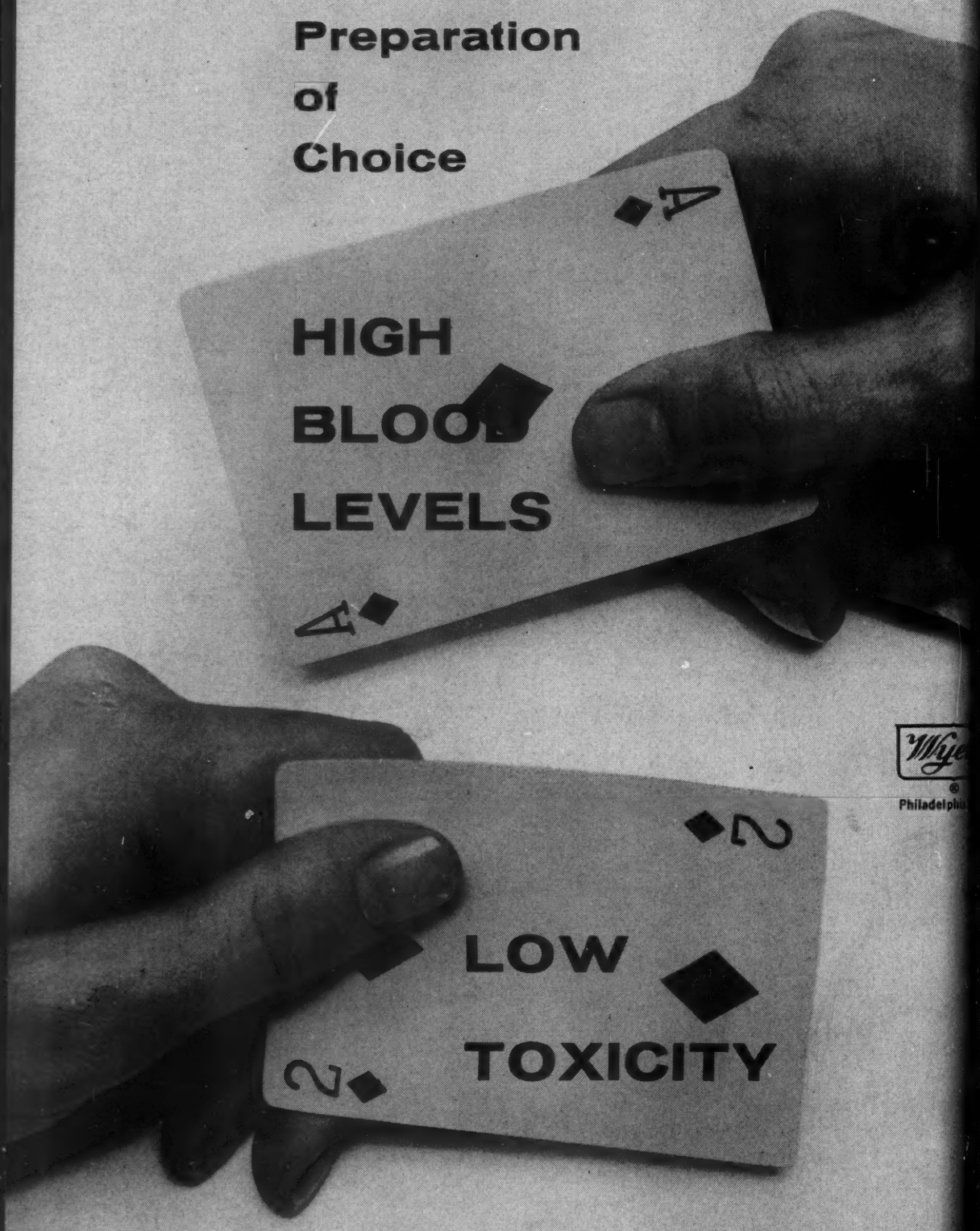

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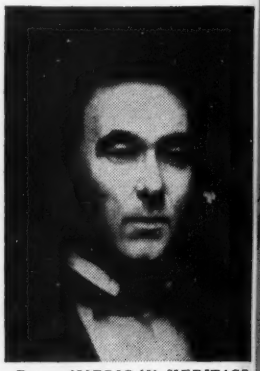

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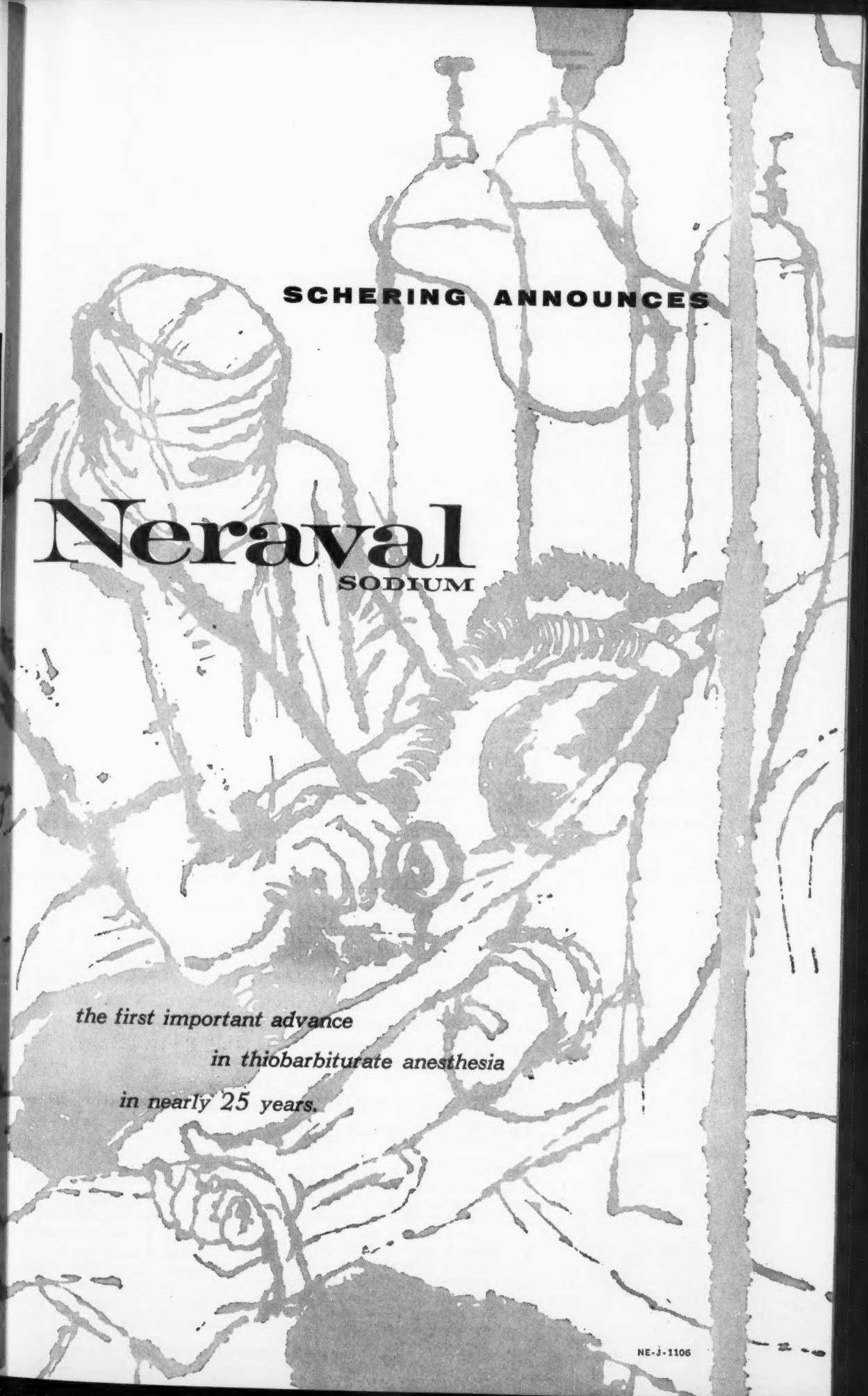
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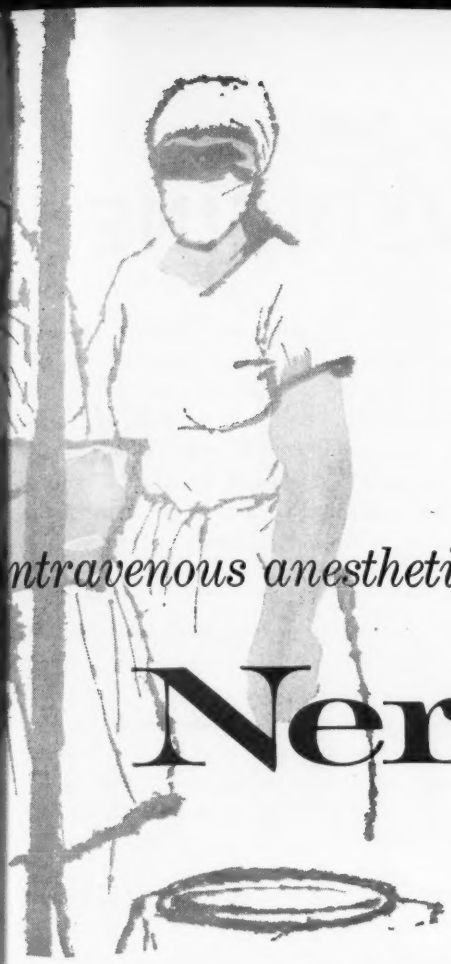

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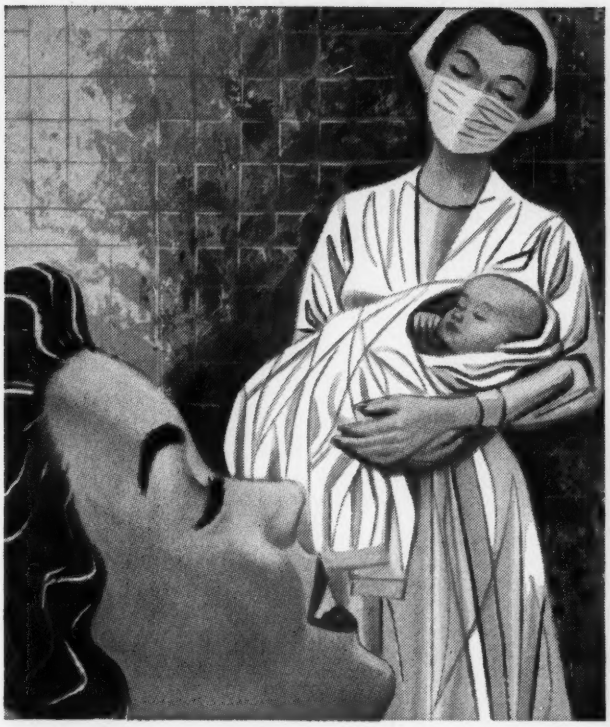

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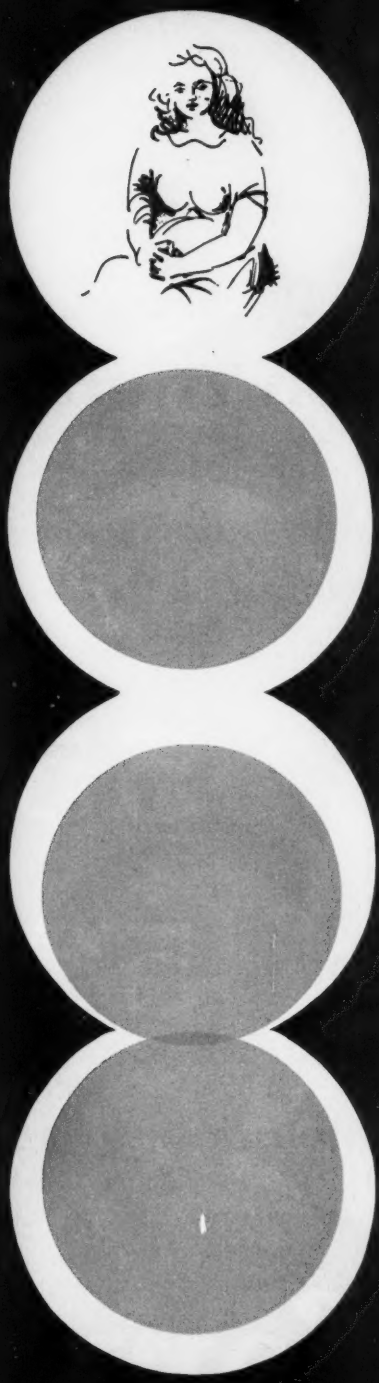

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2. Wagner, H.: Landarzt *31*:496, 1955.
3. Jörgensen, G.: Arztl. Wchnschr. *10*:82, 1955.

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Procedure for the Interpretation of Multiple Precordial and Unipolar Limb Leads.
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D.
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Summary of QRS-T Patterns in Unipolar Thoracic and Limb Leads.

This work is the outgrowth of previous manuals prepared to supplement the Graduate Course in Electrocardiography given at Wayne University College of Medicine for many years. The objective is an organized presentation of the interpretation of the unipolar electrocardiogram. The only basic physics included is that considered essential to the interpretation of the tracing; controversial theories that do not contribute to clinical analysis have been omitted.

The analysis of the arrhythmias is made from leads that clearly display auricular as well as ventricular deflections; the interpretation of the QRS-T complex is based upon the findings in multiple precordial and back leads supplemented, when necessary, by esophageal and unipolar limb leads. The registration of the normal and abnormal QRS-T complex is based upon concepts developed by Frank N. Wilson and associates and shown to be consistent with experimental and post-mortem findings. These concepts have been presented in detail and suitably illustrated with diagrams as an introduction to clinical analysis. Efforts have been concentrated on a systematic lucid description of electrocardiographic findings in an attempt to make reproduction of tracings unnecessary.

Electrocardiographic interpretation in this manual has been approached as an entity, in order to facilitate description and evaluation of its contribution to Cardiology.

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VOL. 73 FEBRUARY, 1957 NO. 2

Obstetrics

FETAL ANOXIA AND ITS POSSIBLE RELATION TO CHANGES IN THE PRENATAL FETAL ELECTROCARDIOGRAM*

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THE scope and technique of prenatal fetal electrocardiography are still in an early stage of development despite the increased interest of obstetricians and cardiologists in obtaining basic information concerning the reaction of the fetus to changes in its physiological environment.

The development of recording methods has been reviewed by many authors[1-4] and a large number of clinical applications have been suggested by those intrigued with the diagnostic possibilities of the technique. The major source of disappointment in fetal electrocardiography has always been that the prenatal recordings from maternal abdominal leads showed only the initial ventricular deflections or QRS waves, consisting of a single "spike"[6-11] or sometimes a small diphasic wave.[5] Fuller complexes have not been convincingly demonstrated. Prenatal fetal electrocardiograms have been rightly considered inadequate representations, in the sense that only one portion of the complexes has been recorded. To be of diagnostic value the graphic records must present not merely the rate and rhythm of the fetal heart but full testimony as to the various components of the complexes and their timing. Workers in this field have, therefore, drawn the general conclusion that the full description of recorded fetal complexes and their significance awaits further improvement in technique and then careful study with more sensitive apparatus.[1, 12]

*Project supported by a Research Grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

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The previous factors limiting the recording of fetal prenatal complexes are of two kinds, (1) those of fetal cardiac origin, and (2) certain extracardiac factors including technical recording problems. Arrhythmias, mostly premature ventricular contractions, are frequently found in the apparently normal fetal heart[13, 27] and these must be recognized and evaluated. Alterations in the position of the fetus within the uterine cavity or, more precisely, alterations of the position relationship of the fetal heart to the maternal abdominal electrodes influence the character of the recordings when no standard pattern of electrode placing is used. Other variable cardiac factors affecting the direction of the electrical axis of the fetal heart include the relative thickness of the right ventricular mass as compared to the left in the fetal heart. This factor has an influence on the difference of repolarization of the ventricles. The position of the heart within the fetal thoracic cavity undergoes modification during intrauterine life and this variation may be reflected in the recordings. Extrauterine factors affecting the accuracy of the fetal electrocardiogram include: (1) nervousness on the part of the patient, producing somatic muscle tremor and respiratory "wandering," (2) insulating effects of amniotic fluid, vernix caseosa,[14] and the soft tissues of the uterus and abdominal fat and muscle. Foremost among the technical difficulties involved in the instrumentation requirements are: (1) insufficient sensitivity of recording apparatus, (2) inadequate control of frequency response to permit attenuation of low interference frequencies, and (3) extraneous interference from electrical sources and amplifier base-line "noise."

The present study results from the development of specially designed and more sensitive equipment which has made available both oscilloscopic monitoring and continuous camera recording of fetal prenatal electrocardiographic complexes capable of analysis. The fetal electrocardiographic variations obtained suggested the attempt to correlate these changes with those clinical conditions in which fetal intrauterine anoxia plays an important part.

Intrauterine and neonatal death from anoxia presents a formidable problem to the obstetric clinician. It is extremely difficult to establish an accurate statistical assessment of the incidence of fetal anoxia in perinatal mortality and morbidity. Clinical analysis must be correlated with histopathologic findings which are often nonspecific.[15] Despite these limitations, however, a relationship between fetal anoxia and the incidence of stillbirths and neonatal deaths has been clearly recognized.[16, 17]

The immensity of the problem of fetal intrauterine and neonatal anoxia has been stressed by a symposium held under the auspices of the Council for International Organization of Medical Sciences.[18] Attention was focused on those cases in which anoxia might be considered a primary cause of death and not merely a terminal event. It was concluded that interference with fetal oxygenation during intrauterine and early neonatal life remains a principal cause of fetal and neonatal death. Fetal mortality and morbidity from anoxia[19] are two of the most challenging and ill understood problems of fetal pathology.[20] The intervention of fetal intrauterine anoxia is a complicating factor in the management of a variety of obstetric conditions. In these conditions the gradual or abrupt change from the stage of reversibility to that of

irreversibility associated with the decline of fetal blood oxygen levels cannot as yet be clinically recognized. At present the obstetric clinician is forced to rely upon changes in the rate and rhythm of the fetal heart sounds and the passage of meconium in cephalic presentations for the diagnosis of intrauterine anoxia. These signs are often late signs and their significance is naturally subject to wide variations of personal interpretations. Active intervention in pregnancy or labor, on purely fetal indications in the presence of possible fetal anoxia, presents a difficult and delicate problem of judgment in a question of balanced risks for mother and child. Earlier and more decisive evidence of impending or actual fetal anoxia must be available if any reduction is to be obtained in the intrauterine and neonatal death rates from anoxia.

The present study was undertaken to establish and determine possible prenatal electrocardiographic criteria for intrauterine anoxia in relation to the following problems: (1) the early recognition of fetal anoxia in labor; (2) the assessment of the intrauterine condition of the fetus in relation to possible cardiac changes induced by fetal myocardial anoxia in cases of toxemia of pregnancy and maternal hypertensive dicsease; (3) the study of anoxia as a factor in postmaturity.

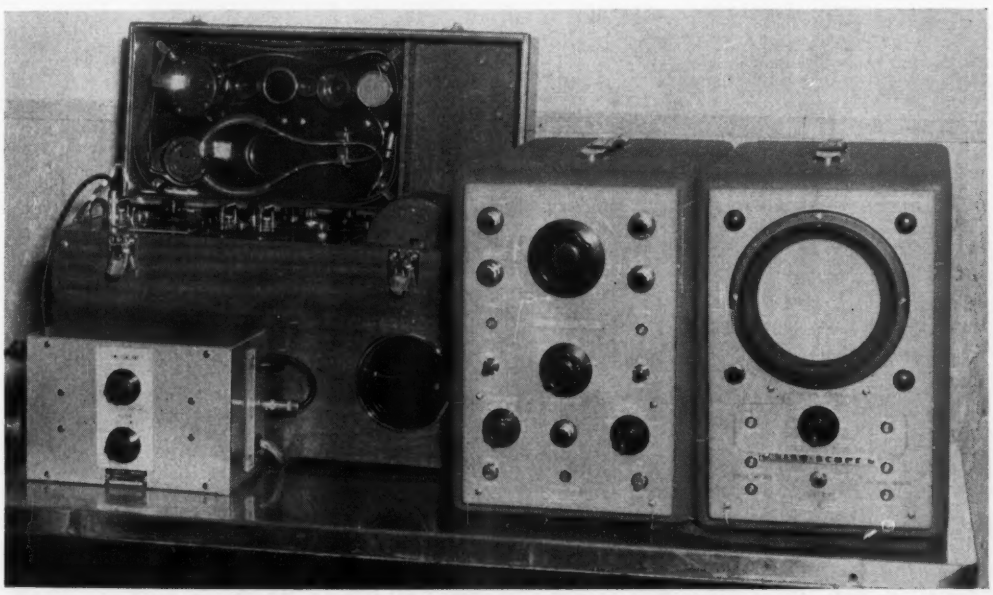

Fig. 1.—Apparatus. Vector system, oscilloscope, filters, and recording unit. (Sanborn.)

Methods and Apparatus

The apparatus comprised a vector system (Sanborn 185) with two amplifier channels, a lead selector system with facilities for both connections and an oscilloscope (Sanborn 169) for visual display of the leads selected. The amplifiers provided gains up to 25 cm. per millivolt input. A special filter network provided low frequency cut-offs in steps to minimize respiratory wandering and extraneous interference when necessary. The specially built-in feed network and filter networks were interposed between the vector system and the oscilloscope, permitting control of both visual display and recording

units. The recording unit consisted of the Sanborn Twin-Beam Cardiette (Model 62), comprising a photographic recorder with a deflection speed of 1 millisecond. Amplifiers provided for separate or simultaneous fetal phonocardiographic and electrocardiographic recording (Fig. 1). The lead electrode positioning and technique of recording followed the pattern of previous experimental experience[4] (Fig. 2).

Oxygen saturation studies were performed from the umbilical cord blood at birth by gasometric analysis in specific cases using the Van Slyke method.[21, 22] Oxygen saturation of umbilical artery and vein blood were determined from blood samples collected anaerobically from isolated cord segments by the method described by Austin and associates.[23]

Results

A total of 96 patients made up the series. Recordings were obtained at various stages of pregnancy and during labor. Sixty-two per cent were multiparous; the age distribution varied from 17 to 40 years. Obesity was disregarded as a contraindication to recording. Positive fetal electrocardiograms were obtained in 94 cases, the 2 remaining patients gave birth to stillborn infants. The series was divided in the following groups:

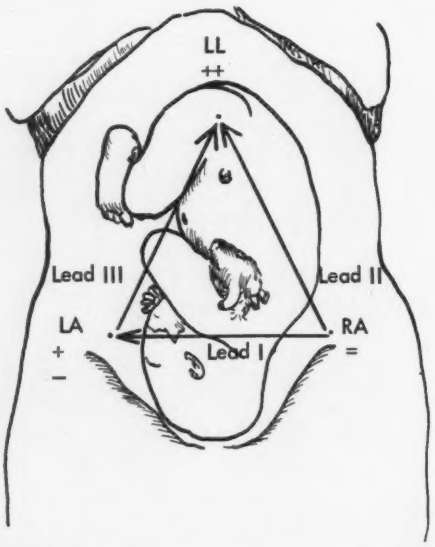

Fig. 2.—Current flowing in direction as indicated by arrows produces an upright deflection of the fetal electrocardiogram for each lead in cephalic presentations. Electrode positions.

Group I. Controls. Electrocardiograms Obtained in Normal Late Pregnancy and Labor.—Fetal electrocardiographic patterns, studied by taking three abdominal leads in late normal pregnancy or in the first stage labor, were obtained in 46 cases. The average fetal heart rate was 127 beats per minute, ranging from 101 to 147 beats per minute. Fetal complexes were rapid. The P wave had an average amplitude of 0.05 mm. and the P-R intervals were 0.06 second duration. QRS deflections showed an average amplitude of 8 to 10 mm. with a duration of 0.02 to 0.04 second. The S-T segment duration was 0.09 second and T waves (when observed) were of 0.03 mm. amplitude (Lead I).

All the patients gave birth to living babies at or about term. The infants cried well at birth and showed no evidence of anoxia. Minimum inhalation anesthesia was employed for delivery.

Gasometric studies were performed on the arterial cord blood at 2, 4, 8, and 10 minutes after birth in 30 cases. The average variation of arterial oxygen saturation within 2 minutes of birth was 47.5 ± 5.1 per cent (number following signs represents the standard error of means). At 10 minutes after birth the average arterial oxygen saturation was 78.5 ± 2.1. The electrocardiographic patterns and oxygen saturation levels in this group were used as a base line for assessment of variations.

Group II. Fetal Distress Series. Effects of Intrauterine Anoxia Upon the Fetal Electrocardiogram.—Records were made in 22 cases of clinically suspected fetal intrauterine distress in labor upon patients at term. The following clinical criteria were employed as a basis of comparison:

1. Progressive slowing of the fetal heart rate to 100 beats per minute between uterine contractions.
2. Irregularity of rhythm associated with a drop in the fetal heart rate to 100 beats per minute or below.
3. Passage of thick meconium in other than breech presentation.

In labor, alterations of the fetal relation to the maternal abdominal electrodes and increased somatic tremor were noticed in some cases. A spontaneously variable fetal pattern was observed in 3 cases when recording in labor.

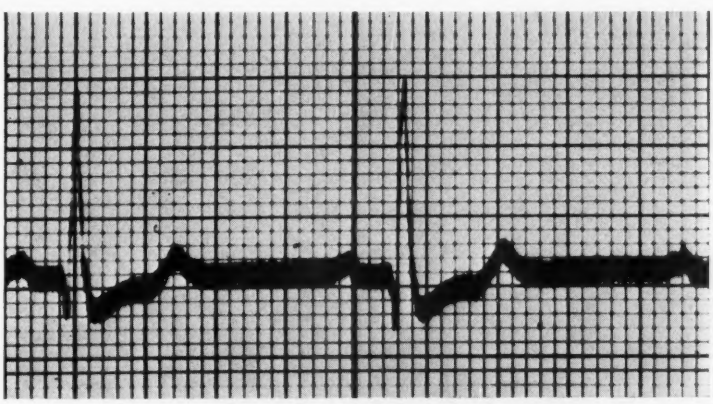

Fig. 3.—Prenatal fetal electrocardiogram in fetal anoxia (enlarged). Depression of S-T segment in Lead I. Fetal heart rate 92 beats per minute.

Certain constant characteristics, however, were noted in the fetal electrocardiograms in fetal anoxic states. The average fetal heart rate was 102 beats per minute. The P wave had an increased average amplitude of 1.1 mm. and the P-R interval was lengthened to 0.12 second duration. QRS complexes showed a reduced voltage and an average duration of 0.06 second. S-T segments were isoelectric or depressed in 75 per cent and had an average duration of 0.12 second. T waves were lowered or inverted in Leads I and II in 35 per cent (Table I).

The earliest changes in the electrocardiographic pattern of the fetus in the presence of anoxia were in the S-T segments and T waves. The changes were considered to be progressive and of possible clinical significance. In severe anoxia the changes consisted of depression of the S-T segment in Leads I and II. Prolongation of the S-T segment and isoelectric or inverted T waves occurred in a high proportion of cases. These changes seemed to parallel the degree of anoxia. The administration of 100 per cent oxygen to the mother did not cause a reversal of the electrocardiographic abnormalities (3 cases). S-T segment variations and T wave changes began before the onset of fetal bradycardia was noted clinically (Fig. 3).

Arterial oxygen saturation studies were performed on 17 infants at the same intervals after birth as on the control series. The average time for the onset of a cry in the group that fulfilled the electrocardiographic criteria for intrauterine anoxia was 7 minutes. At 2 minutes after birth the oxygen saturation of arterial cord blood was 17.1 ± 4.1 per cent and at 10 minutes was 40.5 ± 1.9 per cent.

A case of slow recovery from anoxia associated with prenatal fetal electrocardiographic abnormalities is illustrated in Fig. 4.

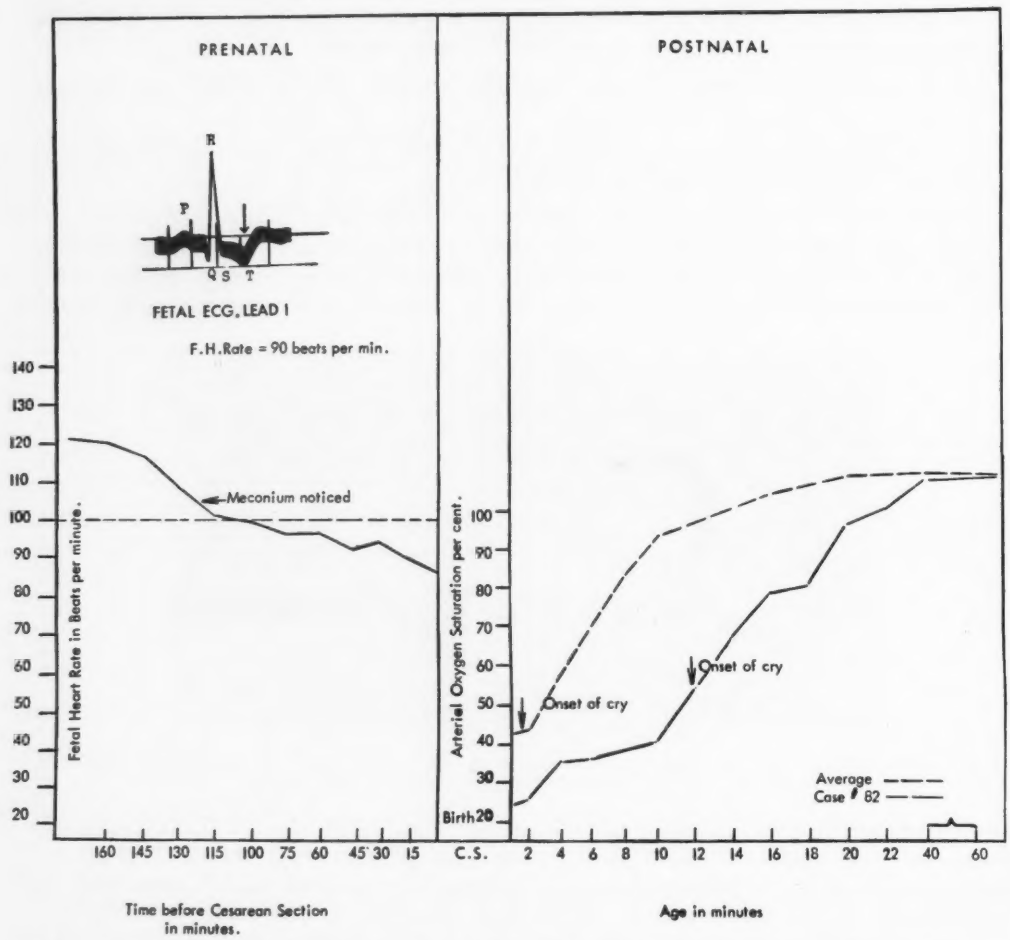

Fig. 4.—Case 82. Clinical and prenatal electrocardiographic evidence of fetal distress related to recovery of the arterial oxygen saturation after birth.

Group III. Influence of Pregnancy Toxemia and Chronic Maternal Hypertensive States on the Fetal Electrocardiogram.—An attempt was made at assessment of the intrauterine condition of the fetus in 12 cases of toxemia of pregnancy and 8 cases in which maternal hypertension complicated pregnancy. Recordings were made at various stages of gestation, ranging between 30 weeks and term. The clinical severity of toxemia, the duration of signs, the levels of hypertension, edema, and amount of albuminuria, had no apparent relationships to the fetal electrocardiogram. Variations in the QRS complexes and the timing of the P-R and S-T intervals were not significant. The estimation of

the optimum time for termination of pregnancy in the interests of the fetus was not indicated by electrocardiographic changes which might be interpreted as due to progressive anoxia in these conditions.

TABLE I. PRENATAL ELECTROCARDIOGRAPHIC VARIATIONS OF THE FETUS IN (1) NORMAL LABOR, (2) FETAL DISTRESS, AND (3) POSTMATURITY, CORRELATED WITH THE LEVELS OF ARTERIAL OXYGEN SATURATION IN CORD BLOOD TWO MINUTES AFTER BIRTH
(The numbers following the ± signs are the standard errors of means.)

AVERAGE ELECTROCARDIOGRAPHIC VARIATIONS, LEAD I	NORMAL VALUES	VALUES IN FETAL DISTRESS	VALUES IN POSTMATURITY
Arterial oxygen saturation per cent (2 minutes after birth)	47.5 ± 5.1	17.1 ± 4.1	30.1 ± 3.1
Fetal heart rate (beats per minute)	127	102	118
P wave amplitude	0.05 mm.	1.10 mm.	0.71 mm.
P-R interval duration	0.06 sec.	0.12 sec.	0.09 sec.
QRS complex duration	0.02 sec.	0.06 sec.	0.05 sec.
S-T segment duration	0.09 sec.	0.12 sec.	0.11 sec.
T wave amplitude	0.03 mm.	Isoelectric or inverted in 35%	Isoelectric or inverted in 30%
Direction of T wave	Upright		

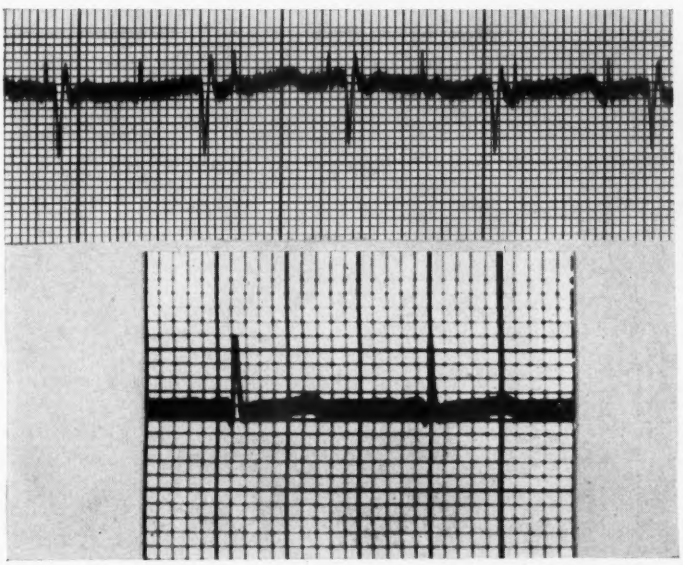

Fig. 5.—Fetal prenatal electrocardiographic complexes in postmaturity: (1) maternal and fetal; (2) fetal complexes (enlarged) showing lengthened S-T segment and low amplitude T wave.

Group IV. The Influence of Postmaturity on the Fetal Electrocardiogram.—The criteria employed for the definition of postmaturity by different authors varies widely.[24-26] Two hundred and ninety-five days after the day of the last menstrual period was adopted as an index in this study. The incidence of postmaturity with this index ranges about 5 to 6 per cent in our hospital obstetric population. Eight cases of postmaturity were examined by prenatal fetal electrocardiography. The fetal heart rates varied from 96 to 140 beats per minute with an average of 118 beats. There was little relationship between the rate and the P waves (average amplitude 0.7 mm.). The P-R intervals varied from the longest of 0.14 second in 4 cases to the shortest

of 0.09 second average in the remaining. QRS complexes in Lead I measured 0.05 second duration. S-T segments were depressed in 3 cases and T waves were small or isoelectric in 3 cases (Fig. 5).

Arterial oxygen saturation studies showed an average percentage of 30.1 ± 3.1 at 2 minutes after birth. In 3 cases there was electrocardiographic evidence suggestive of intrauterine anoxia before birth and the infants in these cases were found to have below average arterial oxygen saturation soon after birth (2 minutes). Fig. 6 shows the rate of increase in the arterial oxygen saturation in (1) Normal control series, (2) Post-mature series and (3) Fetal distress series from age 2 minutes to 12 minutes, together with the pattern of prenatal electrocardiographic variations.

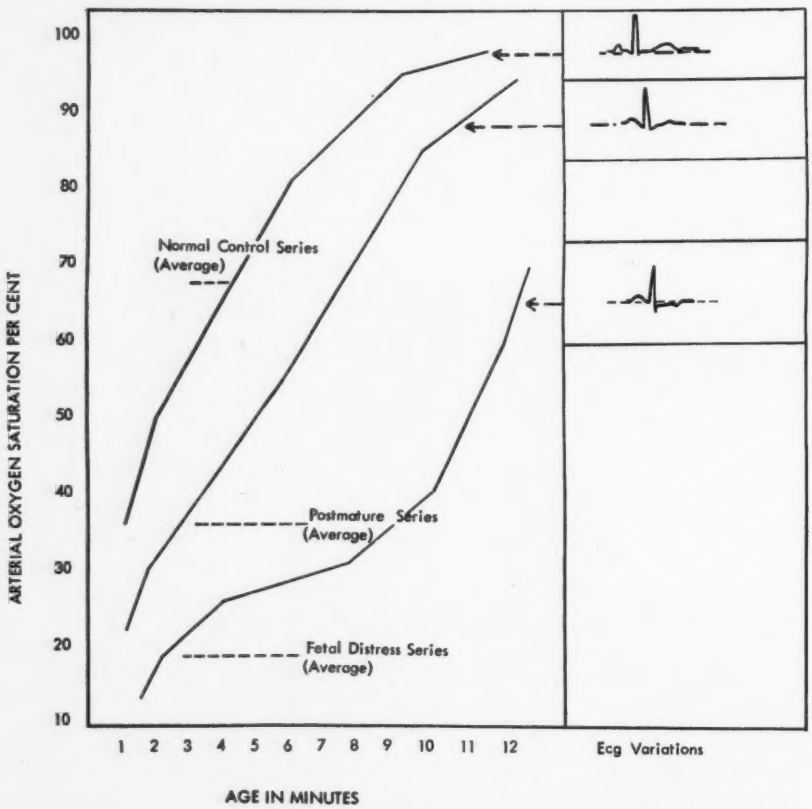

Fig. 6.—Average arterial saturation of cord blood and rate of increase in oxygenation from age 2 minutes to age 12 minutes in (1) control series, (2) postmature series, and (3) fetal distress series. Associated prenatal fetal electrocardiographic variations are shown.

Comment

It has been established that full electrophysiologic heart complexes are present at an early stage of development in the embryonic heart. Hoff and collaborators[28] made excellent records of the electrocardiographic changes during early stages of cardiac development in chick embryos. Records were obtained as early as the 15 somite stage (average of 33 to 35 hours' incubation) and further observations were made as morphologic changes in the growing heart progressed during the differentiations from the primitive cardiac tubes to the coalescence of paired primordia and myocardial differentiation. During the fourth day of incubation, the electrocardiogram adopted a remarkably adult

pattern although at this stage no nerve connections had been made and serial section did not reveal any migrating neuroblasts. The conduction tissue was not histologically distinguishable from the remainder of the cardiac muscle. Kulbs,[29] Robb,[30] and Pollack, Dionne, and Schafer[31] have shown that practically all adult hen electrocardiographic patterns can be obtained from the fourth to the fifth day of incubation in chick embryos. The differentiation of the QRS complex and a slow T wave takes place after about 38 hours of incubation. Microcinematography reveals that the excitation wave is slow.

Direct observations of this kind cannot, of course, be obtained at early stages in human material, but there is now substantial evidence of the characteristics of direct electrocardiograms taken from early living aborted human fetuses and from human fetuses removed at therapeutic termination of pregnancy by hysterotomy at comparatively early stages of gestation. Heard, Burkley, and Schafer[32] used standard limb leads and a chest lead to make electrocardiographic records upon fetuses varying from 9½ to 25 weeks of gestation. Easby in 1934[33] reported an electrocardiogram obtained from a 4½-month-old fetus and Marcel and Exchaquet[34] took leads directly from the exposed heart of a 6 mm. human embryo and showed concordant QRS and T deflections. Raiha[35] examined the electrocardiograms of 45 premature fetuses weighing from 1,000 to 2,500 grams, and indicated that electrocardiographic complexes were recordable directly during embryonic life and followed a characteristic pattern. Mann[36] in 1942 and Vara and Niemineva[37] in 1951 took tracings from the fetus in utero after incision at cesarean section, thus preserving to some degree the intrauterine physiological conditions. Direct tracings revealed a P-Q interval varying from 0.05 to 0.07 second and the QRS complex of 0.02 to 0.03 second. T waves were seen as small deviations from the isoelectric line. Fetal electrocardiograms taken from leads on the maternal abdomen in the same cases showed only a single deflection.

The results of observation on the embryo heart and of direct recordings from the premature heart in the aborted fetus as well as of direct recordings from the uterus, indicated that full cardiac potentials are present from an early stage of human development and that the recording of such complexes at term pregnancy from maternal leads was a problem of improved instrumentation and technique.

Since 1906, prenatal fetal electrocardiography[38] by indirect abdominal, vaginal, and rectal leads has been under investigation and in recent years the rapid evolution of amplification techniques has stimulated renewed interest in the diagnostic application of the method. Mears and Davis,[39] using a six-channel electroencephalograph, reported "composite" patterns of fetal complexes which included the P wave, QRS complex, and T wave. The relationship between fetal electrocardiographic changes, blood saturation of oxygen, and clinical fetal anoxia is a factor which may now become susceptible to more complete investigation. The present study suggests that early electrocardiographic criteria of intrauterine anoxia may be postulated to consist of changes in the S-T segment and T waves which seem to have an association with the reduction of arterial oxygen saturation in fetal blood at birth and with the rate of recovery from the anoxic condition.

The Relationship Between Fetal Distress and Fetal Anoxia in Utero.—There are many important factors related to the complete maintenance of a well-oygenated blood supply to the human fetus. The maternal circulation and oxygenation must be adequate and the deciduoplacental site must be normally developed. Oxygen diffusion across the placenta must be adequate and the circulation in the umbilical vessels must be unimpeded.[40] It has, in recent years, become more generally appreciated that the degree of oxygen saturation of the fetal blood at birth is a vital factor in the survival of the medullary respiratory centers of the fetus. Barcroft[41] in an extensive research into the physiologic mechanism of the initiation of medullary respiratory control, demonstrated the pattern of respiratory failure produced by anoxia and pointed out that anoxia from beginning to end has a depressing effect on the activity of brain cells. Himwich and associates[42] found that if newborn pups inhale pure nitrogen their arterial blood will lose all detectable oxygen in five minutes, yet these animals continue to survive for as much as half an hour or more, this survival being evidenced by some respiratory movement and after that has ceased by cardiac activity for somewhat longer. Electrocardiographic studies disclosed that the heart continues to beat after respiration has apparently ceased. These authors have stressed the part played by fetal blood hyperglycemia which prolongs the fetal anoxic survival time. If the anaerobic use of blood sugar is denied to the animals their survival time under conditions of anoxia is no greater than that of adult animals. The process of death from anoxia was studied in newborn pups by Swann[43] and it was confirmed that circulatory failure in the pups followed respiratory arrest by five to ten minutes. Electrocardiographic recordings were obtained by Bauer[44] from experimental animals subjected to anoxia. He found that bradycardia from anoxia in the rabbit embryo is not brought about simply by reflex vagal action. How should these data be assessed when applied to human fetal physiology?

It has been observed that the human fetus is capable of withstanding anoxia to a remarkable degree and that tolerance to anoxia is many times greater in the human fetus than in the adult. Oxygen saturation studies from blood in the umbilical vein and artery in clinical fetal distress show that fetal survival is possible with very low oxygen saturations (vein 11.6 per cent: artery 2.0 per cent).[40] It has been stated by Brinkman[45] that the human fetus is able to exist by an almost totally anaerobic metabolism for 15 to 20 minutes and under partially anaerobic conditions for much longer. Results of arterial oxygen saturation estimations made by continuous recording from the moment of birth by a modified photoelectric oximeter[46] disclosed that in normal newborn infants the average saturation was 37.9 per cent and at 5 minutes of age was 67.3 per cent, rising to 89.1 per cent at 17 minutes and 94.3 per cent at 2 hours after birth. These readings tend to stress that the normal newborn infant although relatively anoxic at birth has a power for rapid increase in oxygen saturation in the immediate neonatal period.

Under the conditions of the present study, both the values of arterial oxygen saturation shortly after birth and the duration of recovery from hypoxia were depressed in infants who had evidenced electrocardiographic signs of

fetal distress in labor (17.1 per cent). Alterations in the electrocardiographic patterns suggestive of anoxia in utero were seen most frequently in infants whose arterial oxygen saturation lay within 9.1 per cent to 20 per cent at 2 minutes after birth.

Correlation of the incidence of clinical fetal distress with the stillbirth and neonatal death rates has been studied by R. de Soldenhoff and Brill,[47] who found that in a series of 276 perinatal deaths, 50 patients had evidenced the signs of clinical fetal distress before delivery and these deaths were thus classified as "avoidable" on clinical grounds. Fetal distress and its associated problem of fetal death in labor have been investigated by FitzGerald and McFarlane[48] in a series of 3,168 deliveries; it was found that fetal death during labor accounted for 37 per cent of the total perinatal mortality in their series.

It is a relevant fact that there is a greater fetal wastage from anoxia in late intrauterine life than from anoxia in the immediate neonatal period. An estimation of the loss of infant life[49] resulting from or associated with anoxia showed that in 11,147 deliveries intrauterine deaths were 8 per 1,000 births (92 cases) as compared to 1.4 per 1,000 births (16 cases) of neonatal deaths from anoxia immediately after birth. These figures indicate that the greatest area for improvement includes the detection and possible prevention of intrauterine anoxia. It is clear that the figures are interrelated by common factors to the extent that any method that would aid in the detection of intrauterine anoxia would help avoid deaths from anoxia post delivery. The proportionately high incidence of fetal anoxia in late intrauterine life, especially in the first stage of labor, indicates an important avoidable field of fetal loss.

A condition of threatened or actual fetal anoxia in utero was suggested by electrocardiographic means in 22 cases in this study.

Fetal Anoxia in Pregnancy Toxemia and Maternal Hypertensive States.—Pre-eclamptic toxemia of pregnancy and maternal hypertension have a known association with the reduction in the maternal placental blood flow. McClure Browne and Veall[50] estimated the maternal placental blood flow in normotensive and hypertensive women by the use of radioactive sodium as a tracer substance. The result showed that "between the 38th week of pregnancy and term the flow is of the order of 60 ml/minute and in pre-eclamptic toxemia and chronic hypertension there is a reduction to about one-third of this figure." Estimations of the oxygen saturation of the umbilical artery blood in the presence of maternal toxemia show an inadequate or decreased fetal oxygenation.[51]

Various suggestions as to the underlying etiology of uterine ischemia and decreased fetal oxygenation in toxemia have been made.[52-55] The mechanism of placental transfer of oxygen is not yet completely clarified because of the difficulties in assessing the rate of flow in the umbilical circuit, the oxygen content of the fetal blood in utero, as well as the oxygen tension of fetal tissues.

The clinical picture presents the problem of the obstetric management of toxemic pregnancy and hypertensive states. Intrauterine death in these conditions so often remains an unpredictable factor and the optimum time for termination of pregnancy must be based on various considerations including that of the intrauterine condition of the fetus. The clinician is faced with the

problem of judgment as to the point at which the fetus is likely to thrive better in an anoxic environment or in an extrauterine, albeit possibly premature, surrounding. Information concerning the intrauterine condition of the fetus obtainable by electrocardiographic means in this study remains inconclusive so far as this problem is concerned but further work is indicated.

The Factor of Anoxia in Postmaturity.—Functional insufficiency of the postmature placenta for oxygen transfer to the fetus has long been clinically suspected.[25] Objective evidence of progressive intrauterine anoxia when pregnancy continues beyond term has been obtained by recent studies of fetal oxygen levels in prolonged pregnancy.[40] In spite of the adaptations in the oxygen-carrying capacity and the changes in concentration of fetal hemoglobin, there is a progressive reduction in the oxygen content of the fetal blood in postmaturity.[56] A significant difference between the total perinatal death rate in postmaturity and that at term[57, 40] is observed in most studies. The increase in perinatal mortality in association with postmaturity has been attributed by many authors[58-61] mainly to prolonged or difficult labor. In view of the interest aroused by recent knowledge of intrauterine fetal oxygenation, the problem of postmaturity should be reviewed in an attempt to assess the extent that the perinatal mortality in this condition may be attributed to intrauterine anoxia. Nesbitt[26] pointed out, "It is fallacious to attribute total fetal mortality to any single factor such as postmaturity without correcting for associated clinical or pathological conditions that may have been factors contributing to or producing the death." In this connection possible intrauterine anoxia of the postmature fetus may be only a factor to which must be added the risks of prolonged labor, inhalation anesthesia, and possible instrumental delivery. Whatever may be the added risks of difficult labor in postmaturity, the primary anoxic condition of the postmature fetus must add to the over-all mortality.

Investigations into the threat of anoxia per se in postmaturity may be directed toward arterial oxygen studies, research into oxygen transfer, and placental blood flow in these cases. Fetal electrocardiography may give some evidence of the fetal reaction in postmaturity anoxia.

Prenatal electrocardiographic studies in the postmature patients in the present series showed that S-T segment depression was present in 4 cases of the 8 studied, T waves were isoelectric, P-R intervals were lengthened, and these changes were associated with reduction of arterial oxygen saturation in the cord blood at birth (30.1 per cent). These findings are not in themselves significant in this small series but they indicate a field for further observation.

Pathology of Myocardial Anoxia in the Fetus.—The mechanism of the production of electrocardiographic abnormalities in the fetus associated with fetal anoxia is not yet understood. Electrocardiographic changes produced by experimental asphyxia and anoxia in animals seem to have some consistency with the changes found in the human fetus in anoxia. Kountz and Hammouda[62] presented a very complete analysis of electrocardiographic changes in experimental local cardiac anoxia by obstruction of the coronary arteries in animals. These authors demonstrated the S-T segment changes and T wave lowering and

inversion resulting from early direct myocardial ischemia which were strikingly similar to those described in experimental studies of the electrocardiographic patterns in prolonged anoxia in the previable human fetus.[63, 64]

The changes in the human fetus revealed P waves present in all leads. The P-Q time was 0.06 to 0.08 second and this was lengthened to 0.10 second within 15 to 30 minutes after delivery. The S-T segments were isoelectric. The T waves were clearly marked and positive in all leads but became negative after 45 to 60 minutes. Right preponderance was present in all cases. The introduction of oxygen-saturated heparin blood into the umbilical vein caused a rapid and sharp rise in arterial pressure and heart rate and a correction in the electrocardiographic changes. The S-T segment was lengthened at comparable heart rates. T wave inversion disappeared. It has been suggested that the electrocardiographic abnormalities reflect the myocardial ischemia and disturbance in the action potentials induced by the anoxic state[65] but, without further evidence, this can be held only as a theoretical postulate and therefore cannot be interpreted in terms of pathology. Significant work has, however, been done on certain coronary lesions discovered in stillborn infants who have been the subjects of severe anoxia. Gruenwald[66] has demonstrated coronary lesions in the anoxic stillborn infant, resulting in damage to the media and amounting in severe cases to complete destruction with formation of eosinophilic material and debris within the lumen. Examples of transformation of the coronary media into a necrotic mass with cavities filled with granular debris are described. An association is found between these coronary changes and other lesions in the newborn which are commonly interpreted as signs of anoxia. These include hemorrhages into the epicardium and pleura as well as into other tissues and aspiration of amniotic sac contents. The survey showed that necrotic changes in the coronary vessels of the newborn occur more than seven times as frequently in infants with asphyxial hemorrhages in the epicardium as in those without such hemorrhages.

Ahvenainen and Landtman,[67] in a combined electrocardiographic and postmortem study, confirmed both the coronary lesions (10 cases) in the anoxic newborn and the evidence of electrocardiographic changes in the infants at birth. Lesions varied from simple vacuolization of the coronary media with edema of the adventitia to extensive necrosis of the media. The intima was intact, as a rule. Electrocardiographic records in these infants at birth showed S-T segment depression and T wave changes. Newborn infants who survived a period of anoxia showed the complete pattern of electrocardiographic abnormalities in the S-T segment and T waves which reverted to the normal infant electrocardiographic form when the infants had recovered from anoxia. It was suggested that the underlying disturbances of anoxia produced the electrocardiographic abnormalities rather than that the vascular lesions were the primary causal phenomena. The effects of intrauterine anoxia upon the action potentials may, however, result from changes quite apart from possible vascular injuries. Dilatation of the heart with flabby myometrium which can be demonstrated by fat stain to contain large amounts of fat has been observed in association with anoxia[68] and these changes may contribute to the alterations in electrocardiographic records as evidence of direct or indirect effects of anoxia.

Summary

Prenatal fetal electrocardiograms were recorded in 96 gravidas. An analysis of the fetal complexes, their timing and pattern is reported. The characteristics of fetal electrocardiograms in 46 control cases in normal pregnancy and labor were studied.

It is postulated that alterations in the P wave, P-R interval, QRS voltage, S-T segment, and T waves are present in the prenatal fetal electrocardiogram in association with reduced oxygenation of the fetus.

The effects of (1) fetal anoxia and distress in labor, (2) toxemia and maternal hypertensive state, and (3) postmaturity upon the prenatal fetal electrocardiogram were studied and in some cases a correlation made between these variations and the arterial oxygen saturation of cord blood at birth.

The potential role of prenatal fetal electrocardiography in the detection of intrauterine anoxia is discussed.

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MATERNAL MORTALITY AT CHARITY HOSPITAL

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THE maternal mortality rate at Charity Hospital was investigated for the past 10 years (1946-1955, inclusive). This period covered 104,703 live births during which time 131 maternal deaths occurred, an incidence of 12.51 deaths per 10,000 live births. All pregnant patients who died in this hospital are listed, including 9 postpartal patients who were delivered at home or in other institutions, 15 patients with septic early abortions, and 2 with ectopic pregnancies. There were no corrections or deletions.

All were clinic patients since no private cases are admitted to this hospital, and all were treated by one of the three obstetrical and gynecological services (Tulane, Louisiana State University, and Independent). That Charity Hospital received the concentrate of this state's obstetrical pathology is illustrated by the fact that 8 of the above total fatal cases were sent here from other parishes or institutions as far distant as 200 miles when they became too difficult to handle in their locality.

Since this hospital can refuse neither admission nor readmission to any patient and signing a "release" is of no significance, many prepartal individuals refuse to attend prenatal clinic regularly or, indeed, at all, but come in only for delivery from our own as well as from distant parishes. Their mistake is amply recorded in the fact that 55 per cent of the mothers who died were patients who had never made even one clinic visit.

The causes and incidence of maternal mortality in this series are listed in Table I.

TABLE I. CAUSES OF MATERNAL MORTALITY, 1946-1955

CAUSES OF DEATH	NO.	DEATHS 10,000 LIVE BIRTHS
Toxemia of pregnancy	36	3.4
Puerperal infection	29	2.8
Hemorrhage	21	2.0
Embolism	14	1.3
Lower nephron nephrosis	7	0.6
Sickle-cell disease	6	0.5
Sudden death	4	0.37
Anesthesia	2	0.19
Neoplasm	2	0.19
Miscellaneous	9	0.81
Total live births		104,703
Maternal deaths per 10,000 live births		12.51

The statistics of the war years (1942-1945) are available for comparison. Only totals of the Obstetrical Unit are included in this comparison (pregnancies of 20 weeks or beyond). Hence, only gestations of five months or more are considered in Table II where these periods are compared and early abortions and ectopic pregnancies treated on the gynecologic wards are deleted.

TABLE II. MATERNAL MORTALITY OF PATIENTS 20 WEEKS OR MORE PREGNANT

	PRESENT STUDY (1945-1955)		PREVIOUS STUDY (1942-1945)	
CAUSE OF DEATH	NO.	RATE PER 10,000 LIVE BIRTHS	NO.	RATE PER 10,000 LIVE BIRTHS
Toxemia of pregnancy	36	3.4	25	12.1
Hemorrhage	19	1.8	11	5.8
Puerperal infection	14	1.3	13	6.8
Embolism	14	1.3	2	1.0
Sickle-cell disease	6	0.5	1	0.5
Lower nephron nephrosis	5	0.4	0	0.0
Sudden death	4	0.3	5	2..6
Anesthesia	2	0.19	2	1.0
Heart disease	1	0.09	3	1.5
Others	10	0.9	4	2.1
Total live births	104,703		19,001	
Maternal deaths per 10,000 live births		10.69		33.68

There is a striking reduction in the total number of maternal deaths in the present study and, as can be seen from Table II, the greatest improvement is the decrease in deaths per 10,000 live births from toxemia and infection. Of secondary importance is the decreased incidence of fatal hemorrhage and heart disease which allows the less frequent causes of maternal death to assume relatively more prominent positions. That deaths from embolism show a slight increase rather than a decrease is probably a false comparison in that undoubtedly some deaths from embolism are included in "sudden death" in the 1942-1945 series.

TABLE III. COMPARISON OF WAR YEARS WITH PERIOD OF PRESENT STUDY

	MATERNAL DEATHS			
YEAR	ONLY PATIENTS PREGNANT 20 WEEKS OR MORE INCLUDED	ALL PREGNANCIES INCLUDED	LIVE BIRTHS	MATERNAL DEATHS PER 10,000 LIVE BIRTHS
War Years.—				
1942	20		5,350	37.58
1943	19		4,799	39.59
1944	17		4,304	39.50
1945	8		4,548	18.58
Total	64		19,001	33.68
Present Study.—				
1946		14	7,007	19.97
1947		19	8,659	21.94
1948		15	9,407	15.94
1949		9	10,296	8.74
1950		18	10,696	16.82
1951		12	11,316	10.60
1952		16	11,312	14.19
1953		9	11,501	7.82
1954		13	12,093	19.08
1955		6	12,416	4.83
Total		131	104,703	12.51

From Table III it is obvious that with the completion of the war when the staff again became adequate a marked reduction in maternal mortality occurred in spite of the fact that the total number of deliveries has continually spiraled, taxing facilities to their limit. This reduction in maternal mortality is due apparently primarily to an adequate staff, a greater knowledge of toxemia of pregnancy, antibiotics, and the liberal use of blood.

Toxemia of Pregnancy.—

That the late toxemias of pregnancy are still the most important complication of pregnancy in our area is evident from the data in Table I. Some reasons for its prominence in the Deep South are expressed by Ross[1] along with his suggestions for its correction. However, our incidence at Charity Hospital averages approximately 17 per cent in spite of complete hospital and clinic facilities with adequate social and governmental assistance. The hiatus at present seems to be in the area of patient education. They must be taught the necessity of presenting themselves for clinic care even though theirs is apparently a "normal pregnancy," for of the 36 patients who died of toxemia in this series 63.6 per cent did not attend clinic at all. They merely "came in for delivery," or were sent here from elsewhere for serious disease.

There were 22 eclamptic patients in this series and the remaining 14 are classified as having "other toxemias." Significantly, 17 of the above 36 deaths occurred from cerebrovascular accidents and this is the reason sine qua non for the three obstetrical services involved constantly casting about for better methods of controlling the characteristic vasospasm and tissue anoxia of this entity.[2-6] That some measure of success has been accorded the efforts put forth are reflected in the over-all reduction in the number of toxemic deaths as recorded in Table IV. This over-all decrease in the number of deaths is also reflected in the diminution of cerebrovascular accidents which is probably at least partially due to the use of antihypertension drugs.

TABLE IV. DEATHS DUE TO TOXEMIA OF PREGNANCY

CAUSE OF DEATH	DEATHS PER 10,000 LIVE BIRTHS									
	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
Eclampsia	4.3	5.77	2.12	0.9	3.7	1.75	0.0	1.7	2.48	0.0
Other toxemia	4.3	1.15	1.06	0.0	0.0	1.75	2.6	1.7	1.65	0.0
Total	8.6	6.92	3.18	0.9	3.7	3.50	2.6	3.4	4.12	0.0
Cerebrovascular accidents in all toxemia (including cardiovascular-renal disease)	4.2	2.3	2.1	0.0	2.8	1.7	0.8	1.7	1.6	0.0

TABLE V. FATAL PUERPERAL INFECTIONS

Early septic abortions		15
Criminal interruption	10	
Denies criminal interruption	2	
Unknown	2	
Therapeutic abortion	1	
Suppurative thrombophlebitis		6
Bronchopneumonia		2
Pyelonephritis		2
Peritonitis		1
Miliary tuberculosis		1
Generalized Boeck's sarcoidosis		1
Bulbar poliomyelitis		1
Total		29

Puerperal Infection.—

Infection is still the second cause of death in this hospital regardless of effective antibiotics and chemotherapeutic agents. One reason for its prominence is the large number of criminal septic abortions and the significant referral of infected cases from elsewhere. Table V gives the cause and incidence of fatal infection.

Septic Abortions.—The frequency of criminal abortions is the single major factor that causes infection to maintain such a prominent position in maternal mortality tables of this vicinity. The relative ineffectiveness of antibiotics in these instances probably can be explained by at least two factors. First, there is usually dead placental tissue present with little or no blood supply that is an excellent pablum for bacteria and yet impossible to sterilize by blood-borne antibiotics. Second, due to the nature and cause of the infection, these patients wait until they are acutely ill before presenting themselves for treatment and consequently have an overwhelming infection on admission.

Two patients in this group denied criminal interference although this was suspected, and two charts failed to note whether or not this probability was present. The only therapeutic interruption listed in Table V was performed at another institution for severe renal infection at fourteen weeks. The patient subsequently developed postabortal sepsis originating in retained placental tissue and died from septic pulmonary infarcts in spite of massive antibiotic therapy.

Suppurative Thrombophlebitis.—There are 6 definite cases in this group. It is a tribute to the alertness of the resident staff that more deaths have not occurred due to thrombophlebitis in this series. Its ready recognition and the prompt institution of therapy and staff consultation undoubtedly resulted in the above achievement. Only 2 deaths in Table VI can be classed as preventable. One patient was probably discharged with a low-grade infection and the other with retained placental fragments that became a subsequent nidus of fatal infection. All cases were treated promptly and by accepted measures but all had septic pulmonary infarcts on admission and were extremely toxic. Indeed, 2 were in extremis on admission. In addition to antibiotics, pelvic vein ligation has been invaluable in limiting the number of deaths in this group as well as those listed under septic abortions, when done according to the proper criterion as set forth by Collins and collaborators.[12] Unfortunately, it can be noted from Table VI that where pelvic vein ligation was done it was done as a last resort in these instances and not according to the above recommendations.

Miscellaneous.—Into this last, diverse group fall the infrequent causes of fatal infections in pregnant women. Two patients with severe bronchopneumonia died in spite of antibiotics. One developed the infection after a cesarean section for disproportion, while the other was admitted with the pneumonitis. Two other patients died of septicemia developing from pyelocystitis. One was thirty-four weeks pregnant. The disease progressed rapidly and the patient died five days after admission. The second patient had mild diabetes. She was admitted at term with a large baby whose shoulders could not be delivered vaginally until a destructive procedure was done. Bilateral pyelonephritis ensued with renal abscesses and a fatal termination.

The patient who died of peritonitis developed a wound dehiscence after a repeat cesarean section, and the evisceration was not discovered for twenty-four hours. The wound was repaired but she died of infection.

The case of Boeck's sarcoidosis presented a unique problem in that the patient had severe, generalized disease treated here prior to her conception.

However, it was not until she was thirty weeks pregnant that she was referred to this institution again from a town eighty miles distant with extreme dyspnea. She died a few hours after admission.

Miliary tuberculosis was the cause of death in one instance. The patient aborted spontaneously at twenty-four weeks and developed a pelvic infection with pelvic thrombophlebitis. Ligation of the vena cava was done when a pulmonary infarct developed, but she died the next day, probably of her primary disease.

Fatal acute bulbar poliomyelitis occurred once in a primigravida thirty-eight weeks pregnant. She was sent here from a private institution, but her disease was progressive and she died the next day. In almost all of these cases there were preventable factors that are difficult if not impossible to assess. Many of these patients could have been saved by proper management early in pregnancy.

TABLE VI. SUPPURATIVE THROMBOPHLEBITIS

NO.	PATIENT	AGE	GRAVIDITY	PREVENTABLE BY CHARITY HOSPITAL STAFF	TREATMENT	REMARKS
1	E. P.	31	viii	No	Antibiotics	The patient was admitted in extremis and died in less than 48 hours. Pulmonary infarcts
2	E. T.	24	iv	Yes	Antibiotics Vena cava ligation	The patient was admitted and delivered. She developed suppurative thrombophlebitis and antibiotic therapy was begun. Cava ligation done as last resort but fever continued and patient died with pulmonary infarcts
3	W. W.	18	i	Yes	Antibiotics	The patient was admitted moribund with septic pulmonary infarct 12 days post partum
4	M. T.	19	ii	Yes	Antibiotics	Autopsy revealed retained infected placental tissue, lung abscess, septic pulmonary infarct, and suppurative thrombophlebitis when this patient died 12 days after delivery of sepsis. Pituitary necrosis was also found
5	L. S.	19	iii	No	Antibiotics Tetanus antitoxin Vena cava ligation	Admitted with pulmonary infarcts and died after tetanus antitoxin given (skin tested), possibly of anaphylactic shock
6	E. S.	26	iii	No	Hysterectomy Vena cava ligations Antibiotics	Patient four weeks post partum with suppurative thrombophlebitis. Pulmonary infarcts 24 hours later. Surgery completed but death ensued due to sepsis

Hemorrhage.—

The third most important cause of death even in this era of liberal blood transfusions is hemorrhage and it is from this, apparently, that a large portion of preventable deaths occur. These preventable deaths are for the most

part due to errors in judgment inherent in any large training institution regardless of adequate staffs and ready availability of mature physicians. Table VII records the causes and incidence of fatal hemorrhage in this series.

TABLE VII. FATAL HEMORRHAGE

Ruptured uterus	6
Uterine atony (postpartal)	4
Abruptio placentae	3
Abdominal pregnancy	2
"Hemorrhagic diathesis" (afibrogenemia)	2
Ruptured ectopic pregnancy	2
Placenta previa	1
Placenta accreta	1
Total	21

Ruptured Uterus.—This is the commonest cause of fatal hemorrhage. Although preventability is at best difficult to assess, all but 2 of these deaths were definitely preventable. These 2 patients were both moribund on admission while the remaining 4 deaths represent errors of judgment; all are summarized in Table VIII. The advanced parity and age of this group are apparent, as emphasized by other reports.[7]

TABLE VIII. MATERNAL DEATHS DUE TO SHOCK AND HEMORRHAGE FROM RUPTURE OF THE UTERUS

NO.	PATIENT	AGE	GRAVIDITY	PITOCIN	PREVENTABLE BY CHARITY HOSPITAL STAFF	SUMMARY
1	B. G.	38	ii	No	No	The patient was moribund on admission. A cesarean section scar had ruptured at home, 200 miles distant
2	A. S.	29	v	?	No	The patient arrived moribund. The uterus and upper vagina had been avulsed during a forceps delivery at home.
3	J. G.	36	xii	No	Yes	Admitted in labor bleeding vaginally. Diagnosis missed and patient suddenly went into shock and died intra partum
4	R. W.	28	iii	No	Yes	Admitted with brow presentation and delivered after prolonged labor and amniotitis developed. Midforceps used for delivery. Ruptured uterus diagnosed and hysterectomy done but patient died in shock
5	E. B.	36	vi	No	Yes	Normal spontaneous delivery with postpartal hemorrhage. Ruptured uterus diagnosed and hysterectomy done but the patient died in shock. Blood loss could not be replaced rapidly enough
6	A. N.	32	v	No	Yes	Patient with shoulder dystocia delivered and ruptured uterus discovered. Subtotal hysterectomy done but bleeding continued from the portion of the uterus remaining. Bilateral hypogastric artery ligation done but she died of uncontrolled hemorrhage

No patient in this group received Pitocin although this drug is in wide use at our institution. Its safety is due to the fact that an intern, resident, or medical student is at constant bedside attendance while the drug is being given. In addition, it is administered in a manner imitating normal labor rather than a certain amount per unit of time. Individuals vary markedly in their response to Pitocin.

Uterine Atony.—Of the 4 deaths from uterine atony at least 3 were preventable. Here also advanced age and parity are the most important factors. These hemorrhages were sudden, unexpected, and uncontrollable despite oxytocics and emergency measures. Table IX summarizes these cases. The first case illustrates the need for instantaneously available whole blood. Perhaps low-titer, Rh-negative blood processed and ready to give would partially solve this problem since it could be given to anyone and could eliminate gross error in typing due to the press of emergencies as happened in the third case. However, this type of transfusion should be used only in dire emergencies as a lifesaving measure. The second patient was beyond help when she arrived and the third apparently needed more blood initially and should have had a hysterectomy earlier.

TABLE IX. UTERINE ATONY

NO.	PATIENT	AGE	GRAVIDITY	PREVENTABLE BY CHARITY HOSPITAL STAFF	SUMMARY
1	M. C.	35	xii	Yes	The patient had had an uneventful delivery; later a sudden, massive postpartum hemorrhage occurred. The resident was not called in time. The patient could not be given any of the available blood. A hysterectomy was done
2	E. L.	28	?	No	Delivered outside and 2 hours later admitted in profound shock. Died although 4,000 c.c. of blood was given and hysterectomy was done
3	M. F.	40	xii	Yes	Delivered and bleeding progressed. Incompatible blood was given. Hysterectomy to no avail and the patient died in shock
4	G. V.	35	xi	Yes	Normal spontaneous delivery with bleeding and shock which continued in spite of transfusions and hysterectomy. Died of blood loss

Abruptio Placentae.—The 3 fatal cases in this group could well have been placed in the toxemia series since in all the abruptio placentae was merely a complication of pre-eclampsia. Their deaths, however, were directly related to the placental separation and they received the added emphasis accorded the seriousness of these emergencies by being considered alone. Little could be done to help these patients once they arrived.

CASE 1.—An unregistered, 29-year-old Negro woman, gravida x, was near term when she was admitted in shock with pre-eclampsia and a massive abruptio placentae. Transfusions and cesarean section-hysterectomy to control shock were without result. The patient continued to bleed from raw surfaces and died.

CASE 2.—An unregistered 35-year-old Negro woman, gravida x, had pre-eclampsia and was referred here from a town 50 miles distant with massive abruptio placentae and in profound shock. The patient "breathed three times after admission," and an immediate postmortem section was done without success.

CASE 3.—This unregistered, 37-year-old Negro woman, gravida iv, was sent to us from elsewhere at twenty-four weeks' gestation with abruptio placentae secondary to severe pre-eclampsia and hypertension. Cesarean section-hysterectomy was done but her condition deteriorated progressively and necropsy revealed bilateral necrosis of the renal cortex, ascaridiasis, and possible sickle-cell disease.

Abdominal Pregnancy.—There were 2 deaths due to abdominal pregnancies. The first was that of a primigravida in whom an accurate diagnosis was made at term and a laparotomy done. The fetus was obtained and the placenta left in situ. However, after operation was completed, bleeding from the placental site developed and a second laparotomy was done in an attempt to control the hemorrhage. Bleeding continued in spite of all measures with fatal results.

In the second patient the placenta was attached to the anterior abdominal wall below the umbilicus and the operator incised the placenta upon opening the abdomen. All measures used were to no avail and the patient was promptly exsanguinated. Neither of these is judged a preventable death.

"Hemorrhagic Diathesis."—Both these deaths occurred in 1950 before fibrinogen was available and without doubt they are classic cases of afibrinogenemia complicating pre-eclampsia, and premature placental separation. The patients continued to bleed from all raw surfaces regardless of transfusions until death occurred from uncontrolled blood loss.

Ectopic Pregnancies.—There are only 2 deaths in this series during the past ten years, the first of which resulted from a ruptured interstitial pregnancy treated on another service for twenty-eight hours before the gynecology service was consulted. Once consulted, a hysterectomy was done one hour later and the patient did not respond. A marked tachycardia persisted and it was felt that imperfect ligation of a bleeding vessel might be the cause. An exploratory laparotomy was done thirty-eight hours following the subtotal hysterectomy. However, no free bleeding was found. The patient developed basal râles and died suddenly ten hours later in cardiac failure.

The second patient arrived in extremis. An obvious ruptured ectopic pregnancy was present and laparotomy was done on admission. A ruptured right tubal pregnancy was found and removed but the patient was in irreversible shock and died. This death could not be prevented by this staff, but the first ectopic death was preventable.

Placenta Previa.—The only patient lost in this category was one who died suddenly after cesarean section under local anesthesia. The only positive finding at autopsy was an anomalous right subclavian artery. The cause of death was listed as shock. There was one other patient with placenta previa who died but that case is summarized in the sickle-cell disease group.

Placenta Accreta.—This patient was admitted in shock after having been delivered elsewhere the previous day. A total hysterectomy was done with replacement transfusions under spinal anesthesia and the patient died in irreversible shock. This was a preventable death.

Embolism.—

It will be noticed from Table II that the incidence of pulmonary embolism has not changed significantly since 1942. In this group are presented the statistics of the "bland" emboli of phlebothrombosis, amniotic fluid emboli, and a single case of air embolism. Septic clots have previously been considered under thrombophlebitis. Preventability is especially difficult to judge in this group but there seem to be several instances of definitely preventable factors. Table X summarizes all cases.

TABLE X. EMBOLISM

NO.	PATIENT	AGE	PREVENTABLE FACTORS	GRAVIDITY	AUTOPSY	SUMMARY
Bland Embolism.—						
1	C. E.	29	0	vii	Yes	Patient admitted with lower abdominal pain at 36 weeks and died suddenly undelivered. Autopsy showed pulmonary embolism and renal tuberculosis
2	J. R.	33	+	i	Yes	Left inguinal abscess at 20 weeks' gestation caused this chronically ill patient to be admitted. Lumbar sympathetic block done and 10 minutes later the patient died. Autopsy
3	I. D.	23	0	i	Yes	Cesarean section for severe pre-eclampsia and the patient died suddenly in late postoperative period. Autopsy
4	S. S.	27	0	v	Yes	Admitted with mild toxemia and sectioned for disproportion. Evisceration occurred and was closed. Embolism occurred after patient returned to ward
5	M. H.	32	+	ix	Yes	Admitted in labor with membranes ruptured for four days. Transverse lie present and combined version done. Uterus ruptured and hysterectomy done. Saddle embolus occurred at end of hysterectomy
6	E. C.	34	0	xiii	Yes	Uneventful elective section for diabetes. Suddenly died on tenth postoperative day
7	I. B.	14	0	i	Yes	Adolescent with brow presentation in labor. Cesarean section. Patient died suddenly without warning on second postoperative day
8	L. L.	33	+		No	Pulmonary embolus secondary to phlebothrombosis of left leg occurred on second day after cesarean section.
9	R. A.	26	+	vii	Yes	Intrapartum spontaneous rupture of the uterus diagnosed and immediate section done and live baby obtained. Morbid postoperative course terminating with sudden embolus
Air Embolism.—						
1	F. M.	30	+	ix	Yes	This patient had a normal delivery at term except that the placenta was retained 45 minutes and manual removal elected. This was done under ether anesthesia with marked difficulty, when the patient suddenly died
Amniotic Fluid Embolism.—						
1	E. H.	33	0	vi	Yes	Labor began spontaneously and progressed normally. Immediately after an uneventful delivery the patient went into shock and died
2	M. B.	42	0	vii	Yes	Spontaneous labor at term. Contractions very rapid and hard and patient died during delivery in shock. Blood loss negligible
3	D. M.	19	0	i	No	Admitted in labor with twins. Membranes ruptured and cord prolapsed. A breech extraction was done on the first infant and a version and extraction on the second when she suddenly died. Immediate cardiac aspiration revealed clear watery fluid
4	C. P.	35	0	iv	Yes	Patient admitted in labor at term and died suddenly in shock undelivered

Phlebothrombosis With Embolism.—Of the 9 cases in this group, 4 seemed to have preventable factors. All developed thromboses and emboli after surgical procedures except 2 and one of these had a sudden demise within ten minutes of a lumbar sympathetic block. Most age groups are represented and parity is apparently of little importance.

Amniotic Fluid Embolism.—This sudden disastrous type of embolism occurred four times, giving an incidence of 0.37 per 10,000 live births. All occurred during labor or immediately after delivery without warning. One patient had tumultuous contractions, and one case apparently was due to a version and extraction of a second twin which allowed the escape of apparently large quantities of amniotic fluid into the systemic circulation.

That this can occur after the membranes have been ruptured is illustrated by Cases 1 and 4, and is probably due to the amniotic fluid retained as hind waters. It is interesting to note that the 3 spontaneous occurrences were in relatively older women of advanced parity, while the patient in whom the embolism seemed to be induced by the version was only 19 years old and a primigravida. It appears that manipulation and tumultuous labor should be viewed with the possibility of this occurrence in mind.

TABLE XI. LOWER NEPHRON NEHPROSIS

NO.	PATIENT	AGE	GRAVIDITY	ABRUPTIO PLACENTAE	MULTIPLE TRANSFUSIONS	SUMMARY
1	M. B.	34	v	+	0	Sent in from another Parish hospital with severe pre-eclampsia and essential hypertension. Abruptio placentae developed and patient died in anuric phase in spite of artificial kidney
2	V. T.	24	v	+	+	Patient with abruptio placentae and ruptured uterus had subtotal hysterectomy and multiple transfusions. Died of uremia in anuric phase
3	D. B.	36	vii	No	+	Admitted and labor induced with successful delivery but postpartal hemorrhage occurred, necessitating transfusion (reaction) and hysterectomy. A second laparotomy was necessary to control bleeding and the patient died 2 weeks later in the anuric phase. Necropsy revealed pituitary necrosis and adrenal cortical adenoma, and ascaridiasis in addition to lower nephron nephrosis
4	C. R.	33	iii	No	+	Patient admitted for elective repeat cesarean section and a hysterectomy done. Transfusion reaction occurred. Died in anuric phase
5	A. P.	37	ix	No	+	Admitted after 24 hours of labor with infected breech with hydrocephalus. Craniotomy necessary and ruptured uterus occurred. Subtotal hysterectomy done and lower nephron nephrosis occurred. Death in uremia on fifteenth postpartal day
6	V. S.	42	vii	No	+	Criminal abortion was admitted and transfusion reaction occurred. Died in anuric phase
7	M. P.	30	x	No	+	Early septic abortion with transfusion reaction from Rh incompatibility. Died in anuric phase of lower nephron nephrosis

Air Embolism.—This occurred once in this series. It was secondary to a difficult manual removal of the placenta, and is therefore listed as preventable.

Lower Nephron Nephrosis.—

Without doubt the frequent and liberal use of blood increases the hazard of this entity. In this series all patients but one had multiple transfusions with at least one reaction. In Case 7 an Rh incompatibility was obvious on recheck, while, in the remainder, the cause of the incompatibility was less apparent.

The possibility of immunization to little-known or undiscovered blood group factors is increasingly probable due to the frequency of transfusions. Two patients had abruptio placentae and in one (Case 1), this was apparently the sole cause of the lower nephron nephrosis. All patients died in the anuric phase in spite of accepted therapy. The artificial kidney was used in one instance. Table XI summarizes these cases and emphasizes the importance of accurately typed blood even in extreme emergencies. Undoubtedly routine Coombs tests in addition to the cross-match as advocated by Kellner[8] are indicated. At least 6 of these 7 deaths must be classified as preventable.

Sickle-Cell Disease.—

It has been estimated by the Beachams[9] that one out of 5 obstetrical patients with sickle-cell disease dies during pregnancy. They have also illustrated the susceptibility of these patients to infection and thromboses, their poor tolerance of blood loss, and our incomplete knowledge of the mechanism of sickle-cell crises.

In this study one patient with sickle-cell disease died for every 20,000 live births and, as can be seen from Table XII, all died in crises except one patient with placenta previa. She died in shock from blood loss. At least 2 of these patients had severe infections.

TABLE XII. SICKLE-CELL DISEASE

NO.	PATIENT	AGE	GRAVIDITY	CRISIS	SUMMARY
1	F. B.	36	v	Yes	Patient delivered elsewhere at term and sent to Charity Hospital 14 hours later in coma. Course progressively downhill and died in 48 hours. Autopsy
2	B. I.	20	iii	Yes	Patient came to clinic once and did not keep appointment. Admitted at 38 weeks in cardiac failure and died the next day in crisis. Autopsy
3	R. J.	22	i	Yes	Admitted in crisis and died the same day. Autopsy revealed pulmonary infarct
4	S. B.	32	iii	Yes	Admitted at 37 weeks with premature rupture of membranes and living premature infant delivered. Post partum she went into typical sickle-cell crisis—hyperpyrexia, epigastric pain, nausea and vomiting. Death ensued 55 hours later
5	H. T.	34	ii	No	Admitted with sickle-cell disease and pyelitis, when vaginal bleeding occurred at 24 weeks. Placenta previa discovered. Bleeding became worse and section done. The patient went into shock and died in spite of transfusions. Death due primarily to sickle-cell disease
6	C. B.	30	ii	Yes	Admitted at 30 weeks with pyelonephritis and *B. coli* septicemia. Sepsis controlled with antibiotics and patient died at delivery in crisis

It is remarkable, however, that 4 are thirty years of age or older. Usually these patients die at an early age and it is only infrequently that one encounters a pregnant patient with this disease in the fourth decade.

Sudden Death.—

Into this category fall the 3 patients in whom no definite diagnosis could be proved because permission for autopsy was denied. However, in the first 2 cases a presumptive diagnosis of amniotic fluid embolism seems likely. Even though necropsy was not permitted, cardiac aspiration might have given the necessary proof. The other patient had an incomplete history and was not in the hospital long enough for a survey. None was preventable by this staff.

CASE 1.—This 25-year-old Negro woman, gravida x, was admitted complaining of severe and painful contractions. While on the delivery table, intra partum, she had a convulsion, became hypotensive, and died undelivered. Autopsy was denied.

CASE 2.—A 29-year-old Negro woman, gravida v, was admitted and delivered immediately, after which she had a convulsion and suddenly died. Autopsy was denied.

CASE 3.—A 31-year-old Negro woman, gravida iii, was admitted in extremis thirty weeks pregnant after having been acutely ill for one week with chills, fever, and swollen joints. She died suddenly before survey. Autopsy was denied.

Anesthesia.—

Both deaths in this group were due to general anesthesia. One patient died from the aspiration of vomitus under ethylene-ether anesthesia just after a normal delivery. The other was a pre-eclamptic patient who was operated upon for disproportion but who died in the induction period while cyclopropane was being administered.

Miscellaneous.—

Into this miscellaneous group fall the heterogeneous last 11 fatalities, 2 of which were caused by neoplasms. A lymphoma of the anterior mediastinum causing tracheal obstruction at its bifurcation resulted in the death of one patient twenty-eight weeks pregnant, while rupture of a theca-cell tumor in a patient at term with resulting intra-abdominal hemorrhage and death accounted for the second demise in the neoplasia group.

The rest are all single cases. The one patient who died of heart disease had tetralogy of Fallot with pre-eclampsia and she died in failure at twenty-six weeks. Another congenital anomaly (renal hypoplasia) caused death from renal insufficiency at thirty-eight weeks. The individual with acute porphyrinuria was referred to this institution from a local mental institution definitely psychotic. She was a primigravida in whom evisceration followed cesarean section and who died of her primary disease after the secondary closure. The cases of arsenical poisoning and infectious hepatitis have been reported elsewhere.[10] There were two accidents, a patient who suffered burns of 50 per cent of her body surface at six months and another who had a subdural hematoma from a fall in the postpartal period. The diabetic patient in this group had a severe case and was sensitive to insulin. She died in acidosis after prolonged attempts at regulation without results. The last patient had asthma and was asphyxiated by a mucus plug during a severe attack.

No conclusions can be drawn from this last group except to illustrate the number and type of medical and surgical emergencies that may happen to a pregnant individual and cause death. It is surprising that heart disease is so infrequent as to be relegated to this group. However, it merely demonstrates the relative infrequency of severe rheumatic heart disease in our area.

Comment

The maternal death rate at this institution is showing a continuing reduction despite spiraling admissions that tax the facilities of the obstetrical unit to their limit and in spite of the natural gravitation of much of this state's obstetrical pathology to this hospital. Errors in judgment that are inherent in any teaching institution are present in this series, especially in the deaths due to hemorrhage. Many factors seem to play major roles in the declining maternal death rate at this institution. Most important is a well-trained staff sufficiently large to cope with the problems that arise. Patient education is also essential.

In addition, the striking decline of deaths due to toxemia is undoubtedly the result of a greater knowledge of the pathophysiology of this disease, allowing improved methods of therapy. Infection death rates have diminished due to effective chemotherapeutic and antibiotic agents in addition to pelvic vein ligation when indicated.[12, 13]

Ready availability of whole blood induced a reduction in the number of fatal hemorrhages. The advantage of liberal transfusions has, however, caused an increase in the frequency of lower nephron nephrosis which is most often due to transfusion reactions, apparently due, in turn, to blood group factors whose presence is not apparent on routine cross-matching and Rh typing. Hence, the institution of the Coombs test routinely, as advocated by Kellner, in addition to cross-matching and Rh typing, is mandatory especially in patients who have previously been transfused or in whom large and repeated administration of whole blood is being contemplated. In this manner only can incompatibilities due to little known or unknown blood group factors be made apparent.[8]

That the incidence of fatal embolism (except septic emboli) is unchanged is obvious. The largest number of emboli occur secondary to phlebothrombosis, and a further reduction in the incidence of bland emboli is possible only by meticulous observation in the postoperative period. Prophylactic anticoagulant therapy may be indicated in certain complicated obstetrical cases that require long periods of bed rest and especially in those patients in whom evisceration has occurred.

Air embolism is, of course, preventable, and the possibility is always present during intrauterine manipulations, but it must be extremely infrequent. Fatal amniotic fluid embolism developed most frequently in patients of advanced obstetric age and parity, especially in those in whom tumultuous labor was present. The only exception was the youthful primigravida in whom intrauterine manipulation allowed the fatal embolism to occur.

Sickle-cell disease is a grave complication of parturition, and experiences at this institution have been detailed elsewhere.[9] The remaining entities are a heterogeneous group of accidents and diseases that occurred during the period of this study and caused a maternal death. Their limited number permits no conclusions. That heart disease was relegated to this group merely reflects the low incidence of significant heart disease (especially rheumatic heart disease) among the childbearing population in this area.

Summary

1. A ten-year survey of maternal mortality at Charity Hospital during which time there were 104,703 live births is presented.

2. A marked and continuing reduction in the maternal death rate resulting in an incidence of 12.51 maternal deaths per 10,000 live births is recorded.

3. The lowest rate was recorded in 1955 when there were 4.83 maternal deaths per 10,000 live births. There were 12,416 live births during that year.

4. Major factors allowing this decrease were: (a) an adequate, well-trained staff, (b) more advanced knowledge of toxemia of pregnancy, (c) effective chemotherapeutic and antibiotic agents, and (d) ready availability of whole blood.

5. Suggestions for decreasing the incidence of lower nephron nephrosis were presented.

6. The incidence of deaths due to embolism (except septic emboli) was unchanged, and suggestions for its reduction are presented.

7. A diverse miscellaneous group that is too small for analysis was presented in detail.

Appreciation is expressed to Drs. Conrad Collins, Milton McCall, and Adolph Jacobs for their cooperation during this study.

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FACTORS AFFECTING NEONATAL MORTALITY*

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A STUDY has been made of the obstetric complications and prematurity in relation to the neonatal deaths at the Cook County Hospital for the calendar years of 1953 and 1954. It is hoped that a report on this material will be a useful contribution to the rapidly increasing volume of medical literature relating to fetal salvage. There were 22,924 live births during the two years. A larger percentage of maternal complications and approximately twice the percentage of prematurity were found in this medically indigent group as in the State of Illinois as a whole.

The relative incidence of premature labor at the Cook County Hospital was 14.35 per cent in 1953 and 14.16 per cent in 1954 (Table I), as compared with 8.33 per cent and 8.19 per cent prematurity in the hospitals of the City of Chicago and 7.29 per cent and 7.13 per cent in the hospitals throughout the State of Illinois. It will be noted that the percentage of total premature infants at the Cook County Hospital is almost twice that of the State as a whole.

TABLE I. TOTAL PREMATURE INFANTS DELIVERED*

	COOK COUNTY HOSPITAL	OTHER CHICAGO HOSPITALS	STATE HOSPITALS
1953	14.35%	8.33%	7.29%
1954	14.16%	8.19%	7.13%

*From Annual Summaries, Illinois Department of Public Health.

At least one factor in the high concentration of premature babies at this hospital is the long and costly hospitalization required for premature infants. The individual parents find hospital charges prohibitive and free care is a great burden on the charity budget of a private hospital. Consequently, when a premature labor threatens, the patient comes or is directed to the Cook County Hospital even though she may have been registered elsewhere for delivery care.

There are, of course, many factors that bring about the large census of premature infants; not the least of these is the socioeconomic group from which the patients come. This is a medically indigent group and about 88 per cent of the obstetric patients are non-white. The County Hospital accepts all emergencies regardless of whether or not they have previously been booked for delivery. Many have had no prenatal care whatsoever. Some are desperately ill when they are first seen.

It is to be expected that a large charity hospital with a totally unselected group of patients will have more obstetric complications than private hospitals. Table II shows the maternal complications for the two years under consideration. It will be noted that the Cook County Hospital receives almost three

*Presented at a meeting of the Chicago Gynecological Society, Dec. 16, 1955.

times as many cases of intrapartum infection as the other hospitals, and almost four times as many of toxemia. Also, there are more women with antenatal and intranatal hemorrhage, although not as marked an increase is seen in this classification as in the other groups. However, the relatively lower nutritional and consequently lowered hemoglobin level of the Cook County Hospital patients reduces the margin of safety for both mother and baby, in the event of hemorrhage. Often the liberal use of whole blood is all that prevents disaster.

TABLE II. MATERNAL COMPLICATIONS*

	COOK COUNTY HOSPITAL	OTHER CHICAGO HOSPITALS	STATE HOSPITALS
Infection	2.77%	1.02%	0.97%
Toxemia	8.50%	3.17%	2.31%
Hemorrhage	2.39%	1.90%	1.71%

*From the 1953 and 1954 Annual Summaries, Illinois Department of Public Health.

There were 225 live births of infants weighing under 1,000 grams (Table III), of whom 208, or 92.44 per cent, failed to survive the 28 day neonatal period. One hundred twenty-two, or 58.65 per cent, had no discernible maternal cause other than premature labor. The largest maternal factor was multiple pregnancy in 37 instances. Rapid severe labor occurred 5 times. There were 6 mothers with toxemia of pregnancy, one of whom had convulsions. Antenatal hemorrhage occurred 19 times (7 cases of abruptio placentae and 12 of placenta previa). Antepartum or intrapartum maternal sepsis occurred 14 times. Of the remaining 5, one mother had tuberculosis, one was in sickle-cell crisis, 2 had prolapsed cord and small parts, and one had a shoulder presentation.

TABLE III. 225 LIVE BIRTHS UNDER 1,000 GRAMS
208 NEONATAL DEATHS

	PREMATURITY AND ATELECTASIS	CEREBRAL HEMORRHAGE	PNEUMONIA	CONGENITAL ANOMALY	TOTAL MATERNAL FACTORS
Premature labor	111	6	4	1	122
Twins	35			2	37
Precipitant labor	5				5
Toxemia	5	1			6
Hemorrhage	13	5		1	19
Sepsis	14				14
Other	5				5
Total fetal factors	188	12	4	4	208

The only fetal factors recorded in 188 were prematurity and atelectasis; cerebral hemorrhage was found in 12 babies, pneumonia in 4, and congenital anomalies in 4.

There were 362 liveborn infants weighing between 1,000 and 1,499 grams (Table IV) with 154, or 42.54 per cent, neonatal deaths. Again, over one-half, or 82, had no maternal factor other than premature labor. Multiple births were a factor in early labor 19 times, and 10 patients had unusually rapid severe labors. Seventeen mothers had toxemia in varying degrees (2 of whom had eclamptic convulsions). Seven women bled prior to delivery (4 had abruptio placentae and 3 placenta previa). Maternal sepsis was a factor 13 times (one upper respiratory and 12 genital infections). Rh incompatibility was encountered only once, extremities prolapsed 3 times, and there were 2 with polyhydramnios (one of these with multiple fetal anomalies).

TABLE IV. 362 LIVE BIRTHS 1,000-1,499 GRAMS
154 NEONATAL DEATHS

	PREMATURITY AND ATELECTASIS	CEREBRAL HEMORRHAGE	PNEUMONIA	CONGENITAL ANOMALIES	ERYTHROBLASTOSIS	TOTAL MATERNAL FACTORS
Premature labor	68	6	3	5		82
Twins	14	2	3			19
Precipitant labor	9		1			10
Toxemia	13	1	2	1		17
Hemorrhage	6	1				7
Sepsis	9	1	2	1		13
Rh incompatibility					1	1
Abnormal presentation	2			1		3
Other	1			1		2
Total fetal factors	122	11	11	9	1	154

Again prematurity and atelectasis were the only findings in 122 babies, while cerebral hemorrhage was present 11 times. Pneumonia was the cause of death 11 times; there were 9 congenital anomalies, and one death was from erythroblastosis.

In the weight group from 1,500 to 2,499 grams (Table V) there were 2,406 live births with 164, or 6.81 per cent, neonatal deaths. In 90 instances the only evident maternal factor was premature labor. Eleven of the babies who failed to survive were from twin pregnancies, 4 labors were rapid and severe, and 17 mothers had toxemia of pregnancy (2 with eclampsia). Sixteen women bled prior to delivery (2 with abruptio placentae and 14 with placenta previa). Intrapartum sepsis was present in 13 patients (one had pyelitis and 8 of the remaining 12 had prolonged rupture of the bag of waters). There were 4 neonatal deaths following cesarean section. Two were repeat sections in labor, and 2 were done for shoulder presentations in labor. There were 3 cases of Rh incompatibility, 4 abnormal presentations, 3 of which were prolapsed extremities and one was a brow presentation. One mother with cardiac decompensation and thyrotoxicosis, and one with an acute rubeola infection in labor accounted for the remaining 2 maternal complications.

TABLE V. 2,406 LIVE BIRTHS 1,500-2,499 GRAMS
164 NEONATAL DEATHS

	PREMATURITY AND ATELECTASIS	CEREBRAL HEMORRHAGE	PNEUMONIA	CONGENITAL ANOMALY	ERYTHROBLASTOSIS	OTHER	TOTAL MATERNAL FACTORS
Premature labor	53	7	12	15		3	90
Twins	5	3	2			1	11
Precipitant labor	2	1	1				4
Toxemia	7	3	4	1		2	17
Hemorrhage	9	2	4		1		16
Sepsis	6		4	1		2	13
Cesarean section	3		1				4
Rh incompatibility					3		3
Abnormal presentation	2		2				4
Other		1	1				2
Total fetal factors	87	17	31	17	4	8	164

In 87 babies no specific cause of death was given; cerebral hemorrhage was reported as the cause of death 17 times; pneumonia 31 times; congenital anomalies 17 times; erythroblastosis 4 times, and a variety of fetal causes 8 times.

Of the 19,931 term babies who weighed 2,500 grams and over (Table VI) only 106, or 0.53 per cent, died in the neonatal period. No specific maternal factors were observed in 63 instances. Multiple pregnancy was present only once in this term group and rapid, severe labor only twice. Prolonged, dysfunctional labor was a factor 5 times, and it is noteworthy that cerebral hemorrhage was demonstrated at postmortem in 3 of these babies. Seven mothers had toxemia of pregnancy, 2 of them with eclamptic convulsions. There were 7 maternal bleeders, 5 with premature separation of the placenta and 2 with placenta previa. Six mothers had intrapartum sepsis and there were 5 neonatal deaths following cesarean section. Two sections were done for cephalopelvic disproportion, one for dysfunctional labor, and one for bilateral fused hips. One was a postmortem section following the sudden death of a woman in labor. The cause, proved by postmortem, was amniotic fluid embolism and a congenital heart with a patent foramen ovale. The infant lived twenty minutes. There were 5 cases of Rh incompatibility. Two of the breech presentations were delivered spontaneously, and one was delivered by Piper forceps to the aftercoming head. One breech baby died of congenital heart disease, and the cause of the other 2 deaths was recorded as atelectasis. There were 2 cases of prolapsed cords and small parts.

TABLE VI. 19,931 LIVE BIRTHS 2,500 GRAMS AND OVER
106 NEONATAL DEATHS

	ATELECTASIS	CEREBRAL HEMORRHAGE	PNEUMONIA	CONGENITAL ANOMALY	ERYTHROBLASTOSIS	HEMORRHAGIC DISEASE OF NEWBORN	OTHERS	TOTAL MATERNAL FACTORS
None	17	4	15	18		2	7	63
Twins		1						1
Precipitant labor	1	1						2
Dysfunctional labor	1	3	1					5
Toxemia	3	2	2					7
Hemorrhage	1	1	3	1		1		7
Sepsis	2	2	2					6
Cesarean section	3	1	1					5
Rh incompatibility					5			5
Breech	2			1				3
Abnormal presentation			2					2
Total fetal factors	30	15	26	20	5	3	7	106

In this group 30 babies had no recorded cause of death other than atelectasis; 15 died of cerebral hemorrhage; 26 from pneumonia; 20 had congenital anomalies; 5 had erythroblastosis, and 10 deaths were from various other causes.

Maternal factors by weight groups are shown in Table VII. There were no obvious maternal factors in 357, or 56.48 per cent. This percentage remained relatively consistent in all weight groups. Twins occurred 37 times among the tiny babies, 19 times among the middle prematures, 11 times in the

larger prematures, and only once in the term group. Maternal hemorrhage, either antenatal or intranatal, was present 19 times in the smallest group, 7 times in the next, 16 times in the larger prematures, and 7 times in the term group.

Toxemia was a factor 17 times in the two middle groups, 6 times in the smallest, and 7 times in the term babies. Maternal sepsis was present a total of 46 times and rapid labor 21 times, while various maternal factors shown in the previous charts were present 44 times. It is notable that a diversity of factors is more evident in the two large groups.

TABLE VII. MATERNAL FACTORS BY WEIGHT GROUPS

WEIGHT	TOTAL LIVE BIRTHS	TOTAL NEONATAL DEATHS	NONE	TWINS	HEMORRHAGE	TOXEMIA	SEPSIS	RAPID LABOR	ALL OTHERS
Under 1,000 grams	225	208	122	37	19	6	14	5	5
1,000-1,499 grams	362	154	82	19	7	17	13	10	6
1,500-2,499 grams	2,406	164	90	11	16	17	13	4	13
2,500 grams and over	19,931	106	63	1	7	7	6	2	20
Total	22,924	632	357	68	49	47	46	21	44

Fetal factors by weight groups are shown in Table VIII. Postmortems were done in 78.3 per cent of the infant deaths. No specific diagnosis other than prematurity and/or atelectasis was found in 427, or 67.56 per cent. The absence of a specific diagnosis was more common in the two smallest groups; however, in approximately one-half of the larger premature infants, and in one-third of the term babies no specific cause of death was recorded.

TABLE VIII. FETAL FACTORS BY WEIGHT GROUPS

WEIGHT	TOTAL LIVE BIRTHS	TOTAL NEONATAL DEATHS	PREMATURITY AND/OR ATELECTASIS	PNEUMONIA	CEREBRAL HEMORRHAGE	CONGENITAL ANOMALY	ERYTHROBLASTOSIS	ALL OTHERS
Under 1,000 grams	225	208	188	4	12	4		
1,000-1,499 grams	362	154	122	11	11	9	1	
1,500-2,499 grams	2,406	164	87	31	17	17	4	8
2,500 grams and over	19,931	106	30	26	15	20	5	10
Total	22,924	632	427	72	55	50	10	18

Pneumonia was a specific finding in 72 babies, cerebral hemorrhage was present 55 times. Congenital anomalies incompatible with life accounted for 50 deaths. Only 4 deaths due to congenital anomalies were found in the under-1,000-gram group, 9 in the middle premature, and 17 and 20 in the two larger groups, respectively.

Because of the large Negro census, the loss from Rh incompatibility is less than in some series reported. Only 10 infant deaths were from erythroblastosis. A variety of fetal factors proved by postmortem examination, such as toxic hepatitis, gastroenteritis, pneumococcic meningitis, sarcoma, and so forth was present in 18 infants.

There were 10,352 liveborn infants of 1,000 grams and over in 1953 (Fig. 1). The live birth census by months varied from a low of 710 in February to a high of 1,018 in December. The neonatal death rates per thousand live births varied from a low of 9.95 in January to a high of 29.48 in October. The rates for the months of January, March, April, June, July, and August were below 20, while in the remaining six months the rates were 20 or above. The neonatal death rate for the entire year of 1953 was 20.38 per 1,000 live births.

In 1954 there were 12,347 liveborn infants of 1,000 grams and over (Fig. 1). The census varied from a low of 914 live births in February to a high of 1,107 in July. July, with the largest number of births, had a rate of 12.65, the lowest for the year. The highest rate of 25.27 occurred in March. The rates for January, February, June, July, August, and October were 15.77 and below, and for March, April, May, September, November, and December were 16.30 and above. The total neonatal death rate for 1954 was 17.25 per 1,000 live births.

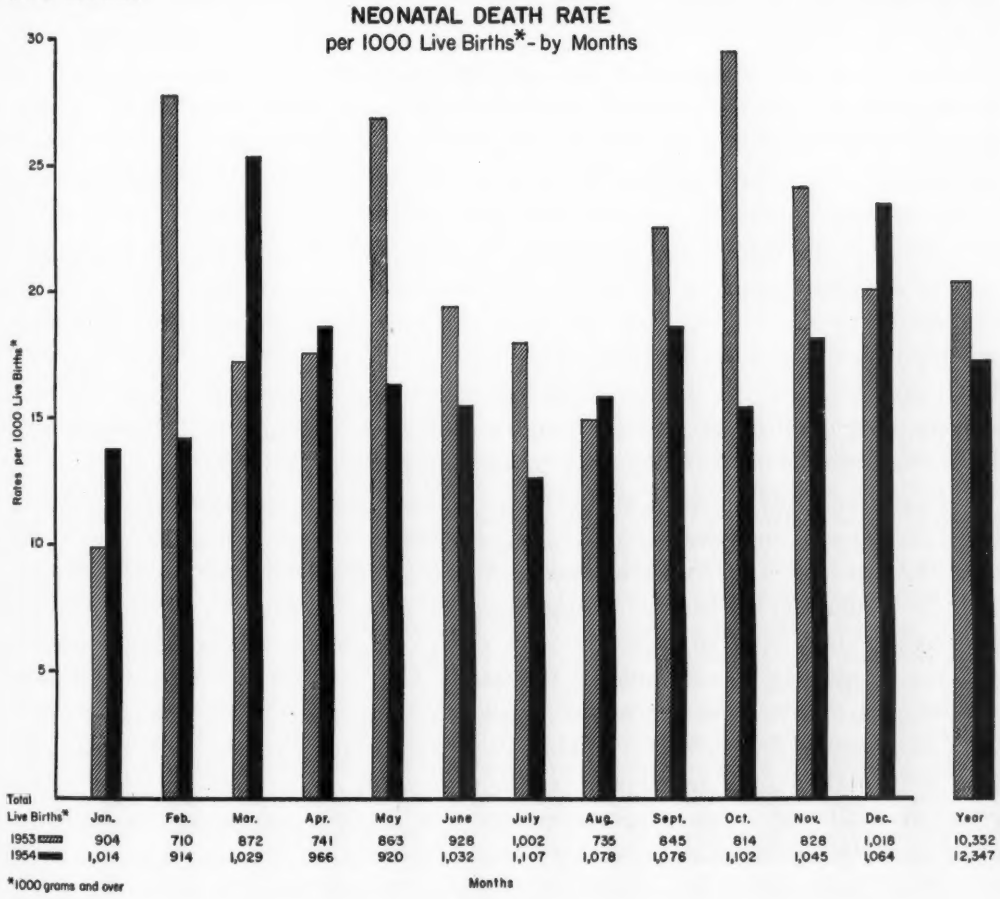
NEONATAL DEATH RATE
per 1000 Live Births*- by Months
Rates per 1000 Live Births*
30
25
20
15
10
5
Total Live Births*
Jan. Feb. Mar. Apr. May June July Aug. Sept. Oct. Nov. Dec. Year
1953 904 710 872 741 863 928 1,002 735 845 814 828 1,018 10,352
1954 1,014 914 1,029 966 920 1,032 1,107 1,078 1,076 1,102 1,045 1,064 12,347
*1000 grams and over
Months

Fig. 1.

There is no seasonal pattern, nor is the rate related to the census. Because of the many variables, rates obtained on studies of 100, or even 1,000 babies, which represent the monthly and yearly births in many hospitals, cannot be given much credence. A few small babies or 3 or 4 severe congenital anomalies can alter the salvage rate of a small series materially for or against a given year.

Admittedly the Cook County Hospital Maternity Division is in need of more space, as well as more nurses and auxiliary personnel. However, the same conditions exist in the good months as in the bad months. Comparable obstetric and pediatric medical care is also given each month of the year. There must be another factor or factors responsible for the marked variation in rates from month to month.

The rate depends upon the number of smaller and/or more fragile babies and the number and severity of maternal complications. Some babies have the innate stamina to cope with extrauterine existence and some do not. If a large number of the more fragile babies are concentrated in a given month, the rate will rise.

This is not to be construed that we believe we have reached or even approached the irreducible minimum of fetal deaths. We recognize the fact that every baby and particularly every premature infant is a specific challenge to both the obstetrician and the pediatrician. Safeguards have been established at the Cook County Hospital to protect premature babies. There is not time, nor is it the purpose of this presentation, to consider the details of premature care. The program followed at the Cook County Hospital is similar to the accepted principles used in other maternities.

We are convinced, after the detailed survey of the charts, that anesthesia and/or analgesia is not a prominent factor in the neonatal deaths at the Cook County Hospital. Less than 12 per cent of all our patients in premature labor receive other than local infiltration anesthesia. In premature labor, analgesia is given only for a specific maternal indication such as toxemia. Reports constantly blame anesthesia and analgesia for fetal damage and fetal death. Neither anesthesia nor analgesia is a significant factor in this series.

Gratifying advances in the care and management of premature infants have been made in recent years. Nevertheless, the best structural facilities, and the most skilled obstetric and pediatric attention is *not good enough.* This is evidenced by the increasing number of children who have survived premature birth only to face life with absent or defective eyesight, varying degrees of spasticity, and mental defects. With certain notable exceptions, the baby is infinitely better off in its rightful intrauterine environment until it is sufficiently developed to enable it to cope with extrauterine existence. The only satisfactory treatment is the *prevention of premature labor.* The greatest challenge to us, as obstetricians, lies in the large group of patients with no maternal complications other than prematurity.

The survival rate of premature infants depends directly upon the birth weight (Table IX). Of the liveborn infants under 1,000 grams, 92.44 per cent died during the neonatal period. In the weight group from 1,000 to 1,499 grams, 42.54 per cent failed to survive. Those babies weighing between 1,500 and 2,499 grams fared better, with 6.81 per cent neonatal deaths. The majority of the deaths in this group were in smaller babies. There were 19,931 liveborn infants of over 2,500 grams with 106 deaths or 0.53 per cent.

TABLE IX. LIVE BIRTHS AND NEONATAL DEATHS BY WEIGHT GROUPS

WEIGHT (GRAMS)	LIVE BIRTHS NO.	NEONATAL DEATHS	
		NO.	PER CENT
Under 1,000	225	208	92.44
1,000-1,499	362	154	42.54
1,500-2,499	2,406	164	6.81
2,500 and over	19,931	106	0.53

Summary and Conclusions

There were 22,924 live births at the Cook County Hospital in 1953 and 1954.

This is a medically indigent socioeconomic group.

Hemorrhage, sepsis, and toxemia are one and a half to four times as prevalent in Cook County Hospital patients as in the other hospitals of the State of Illinois.

Eighty-eight per cent of our patients are non-white.

Thirteen and five-hundredths per cent of the live births were premature (approximately twice as many as in other hospitals in Chicago and in Illinois).

Eighty-three and twenty-three hundredths per cent of the neonatal deaths were in the premature group.

Neonatal deaths can be effectively reduced by *prevention* of premature labor.

55 EAST WASHINGTON STREET
CHICAGO 2, ILLINOIS

Discussion

DR. JAMES E. FITZGERALD.—The number of premature deaths in any institution will depend upon the number of premature deliveries. If your premature deliveries increase, there will be more deaths. There is no possibility of getting away from this fact. At Cook County Hospital, there were 140 prematures per 1,000 live births. In the State of Illinois for the same period, there were 72 prematures per 1,000 live births. It is natural to believe that there should be twice as many premature deaths in Cook County Hospital on the 1,000 live birth basis as in hospitals that have half the number of premature deliveries. It is a fact that the vast majority of babies weighing 1,000 grams or less die. It is also quite evident that the group weighing 1,000 to 1,500 grams have a mortality of almost 50 per cent. In that particular group the mortality is very much more marked in the babies closer to 1,000 grams and improves as the 1,500 gram weight is approached. In the next group from 1,500 to 2,500 grams the mortality drops to 6 per cent. It seems to me that practically all premature deaths occur in babies that are under 1,500 grams and that there should be some new way of looking at our statistics to make sense.

Dr. Webster has shown you that it does not make any difference what month or what year or who is taking care of the patient. In 1954 when the birth rate was higher, the mortality was higher with the same staff delivering the babies and the same pediatric staff taking care of them. There are so many variable factors, all of which show that deaths occur in babies under 1,500 grams. Dr. Dieckmann has some remarks about putting too much effort in the salvage of these tiny babies. It seems to me that what we should get out of this paper is that there should be some way of figuring statistics so that hospitals in Chicago, New Orleans, or New York would be able to say how many premature births as well as how many premature deaths per 1,000 live births they had. It seems to me that if you have twice as many prematures born you are bound to have twice as many prematures die, no matter what the care.

For several years we were drowning prematures in oxygen. We have stopped that but the death rate has not changed. I am interested in having this Society and other similar societies do something about collecting statistics on some other basis. They should be based on the salvage rate by weight groups and not upon the per 1,000 live births. In babies under 1,000 grams and even under 1,500 grams the mortality is half of the deliveries. From there on the mortality figures get increasingly better. We know that at Cook County Hospital the death rate of full-term babies was 0.5 per cent, which is as good as in any institution.

We should start a campaign for a change in the recording of infant deaths and put them on the basis of the salvage rate per number of prematures born rather than on the salvage rate per 1,000 live births, because the present method puts a black eye on any institution that has a large number of prematures. Areas can be selected in which a large number of premature labors are to be expected. These are the areas in which the patients are less well housed, less well fed, and less well educated. These patients congregate in large charity institutions such as the Cook County Hospital. A change in collecting statistics would aid in evaluating an excellent report such as this and would take hospitals such as this one off the hook.

DR. WILLIAM J. DIECKMANN.—This presentation is based on approximately 23,000 deliveries which occurred in two years. It requires almost six years in our institution to equal this number of deliveries. I am uncertain about the reliability of many of our figures as to the complications, causes of death, etc. It makes one wonder about the reliability from such a huge service. Who makes the diagnosis, performs the autopsies, examines the sections, etc.? These comments do not detract from the value of this study.

Their figures for the two years are constant. Fourteen per cent premature, over twice what occurs on our service. I believe the data would be more valuable if the various complications and causes of death were placed on a percentage basis. I wonder why the monthly neonatal death rate ranged from 10 to 29 per 1,000. Ninety-two per cent of the babies who weighed less than 1,000 grams did not survive; I have maintained for years that these babies should be placed in the incubator and let alone for 24 hours. If they survive that period they are worth while salvaging. Forty-three per cent of those weighing from 1,000 to 1,499 grams died, and here, too, there should be a trial period of 24 hours. This would enable the nursing and medical staff to devote more time to the group weighing 1,500 grams or more. There is no question but that every baby's life is valuable, but common sense must be used. Certainly in babies weighing less than 1,500 grams who survive there is a very high incidence of mental abnormalities and other serious defects which not only make life difficult for the child but for the family as well. I often wonder if modern obstetrics and pediatrics are not responsible for some of our dictators, sadistic criminals, etc. There have always been abnormal people but it seems that the number is greater in the Twentieth Century than in any of the other preceding centuries.

In the babies weighing 1,500 grams or more, I believe there are too many deaths due to cerebral hemorrhage, pneumonia, and atelectasis. How can these be prevented? If patients are examined at 26 weeks' gestation and periodically thereafter, beginning effacement of the cervix can be detected and the patient can be placed at bed rest, thus prolonging the pregnancy to 32 to 36 weeks. Deaths from atelectasis, pneumonia, and cerebral hemorrhage can be decreased by better care during labor. No induction should be performed unless the cervix is "ripe." Vaginal examination will determine if the membranes are ruptured, and measures can be instituted to start labor once the cervix is "ripe." I do not believe there is any evidence showing that antibiotics prevent intrauterine pneumonia.

A thousand babies per month seems a huge service, but I have a report from the Maternity in Caracas, Venezuela, of 24,000 deliveries per year. I wonder how reliable their statistics are.

This obstetrical service at the County Hospital is so large and has so much that is abnormal that it is an ideal place to obtain data. In a period of two years, almost any obstetric or pediatric problem can be studied with a sufficient number of cases. The five medical schools in Chicago should support the County Staff with an expert record system for the answer to many of our moot questions.

DR. PHILIP C. WILLIAMS.—It is of interest to compare the fetal neonatal mortality rate at the Cook County Hospital with that of Provident Hospital. Approximately 98 per cent of the patients on the obstetrical service at Provident Hospital are Negro; 75 per cent of the patients are on the private service; 25 per cent, on the clinic service. Many of the patients on the private service may have seen the doctor only once prior to admission or may present themselves in labor requesting the services of the physician who delivered them previously. Again, patients who have had no prenatal care and no private physician are admitted in active labor, too far advanced to make the trip to Cook County Hospital. Thus a fair percentage of our patients belong to the same category as those of the Cook County Hospital group.

For the years 1951 through 1953 (a three-year period), there were 5,815 live births. The relative incidence of premature labor was 12.29 per cent (1951, 11.57 per cent; 1952, 12.57 per cent; 1953, 12.64 per cent). In the hospitals throughout the State of Illinois, the incidence of premature labor for the same three-year period was 7.06 per cent.

As far as maternal complications on the obstetrical service are concerned, Provident Hospital has one and one-half as many cases of toxemia, one-half the number of cases of infection and three-fourths to one time the amount of hemorrhage, as the State's total.

The neonatal death rate per 1,000 live births was 14.78 per cent (1951, 16.78 per cent; 1952, 12.72 per cent; 1953, 14.80 per cent), as compared to 18.11 per cent for the State of Illinois.

There were 28 liveborn infants under 1,000 grams of whom 27 or 96.42 per cent failed to survive the 28 day neonatal period. In the group who weighed 1,000 to 2,499 grams there were 631 live births with 25, or 3.96 per cent, neonatal deaths. Of the 5,166 term babies weighing 2,500 grams and over, only 34, or 0.66 per cent, died in the neonatal period.

As in the Cook County Hospital series, congenital atelectasis and prematurity were the main causes of death in the "under-1,000-grams group." In the remaining groups, a large percentage was due to congenital anomalies in addition to congenital atelectasis. Erythroblastosis fetalis was a factor in only 2 cases.

DR. WALTER DILLON.—Has Dr. Webster any figures on the mortality in male and female infants?

DR. CHARLES FIELDS.—I think somewhere we missed a few points. To begin with, it is important to know that figures Dr. Webster gave as the percentage of fetal mortality at Cook County Hospital compare favorably with those of the City of Chicago as a whole in the all-white groups. It is important to know that the volume that is handled in a purely service hospital is again illuminating. More babies die in the first 48 hours than in the whole year. It would behoove obstetricians to take a little time to salvage those babies regardless of the weight. If you can keep the baby in utero, it has a better chance of survival.

In this large group of maternal factors for premature labor, the etiology of which is unknown, nothing was said about premature rupture of the membranes. What was the management? Were they managed conservatively or was labor induced? Another thing is the conservative management of placenta previa in a baby on the border line of vitality. Finally, what is the obstetrician's role in the management of the baby born in the delivery room? Those of you who are not familiar with the Cook County Hospital cannot understand that a hospital with facilities for delivering 5,000 babies really delivers twice that many in a 24 hour period, and babies are dropping all over the place. The point that comes to me is that the possibility of survival depends upon what happens to that baby in

the first 24 hours. Many things that happen in the first 24 hours happen in the delivery room, with everyone running to take care of emergencies and the baby is left alone. Therefore, it does not get the immediate care so essential to survival.

In spite of the fact that our statistics at Cook County Hospital are as good as for the city of Chicago as a whole, I think there are some places where we could salvage many babies that are now lost, such as the management of premature rupture of the membranes, the care of the baby that is on the borderline of vitality, the conservative management of bleeding, especially in placenta previa. Many babies can be salvaged from bleeding whether it is from placenta previa or abruptio placentae, if we take care of their anemia by immediate transfusion to overcome the blood loss.

On the service, 9 babies were lost from erythroblastosis fetalis and 11 survived. A little attention to the Rh factor and the early replacement of blood might help to salvage some of those babies. The Cook County Hospital is doing heroic work with what it has to work with. Attention to some of these details might even save some of the babies we have lost.

DR. WEBSTER (Closing).—I am very grateful to all of the discussants. Dr. Fitzgerald was for many years Chairman of the Department of Obstetrics at the Cook County Hospital and has firsthand knowledge of the conditions.

In answer to the question regarding male and female distribution of the neonatal deaths, I do not have that breakdown. I hope you all heard the one sentence which says, "This is not to be construed that we have reached or even approached the irreducible minimum." Dr. Fields knows that, and I know it, and Drs. A. J. Kobak, C. O. Smith, Frank Fara, P. J. Stein, and Harvey Gollin and the rest of the Staff, as well as the unsung but all important resident staff, have all worked very hard to try to reduce the number of neonatal deaths. As Dr. Fields said, we have missed some facts in the discussion. This is an understatement of the century. I know all those points that Dr. Fields brought out are worthy of discussion and we are aware of them. However, I had to cut this material to 20 minutes. Through the good offices of Dr. Kobak and Dr. Stein in the last few years we have introduced some better measures for the care of prematures. I have not the time to discuss those in detail.

Some of you have asked about stillbirths. We have about the same number as other people. We are working on a paper on stillbirths at the present time; there were 202 stillbirths in 1953 and 304 in 1954. That gives a rate of 18.9 in the first year and 19.4 in the second year. We get a few more than our share of antenatal dead-on-arrival patients who are transferred from other services to the Cook County Hospital. We have more twins because of the big Negro census. We average one twin pregnancy for every 64 deliveries. We have the group of hard-working, malnourished, poorly housed women who have many children at home to care for, and who do heavy manual labor. These conditions bring about earlier labor, especially in twin pregnancies.

I will conclude by reading one sentence from an article by Dr. Clifford of Boston in *The Journal of Pediatrics,* who quotes Block as follows: "The occurrence of premature births is primarily a public health problem concerned with economic conditions, social conditions and housing."

AMNIOTIC FLUID EMBOLISM, AFIBRINOGENEMIA, AND DISSEMINATED FIBRIN THROMBOSIS

Case Report and Review of the Literature*

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DURING the past decade, the clinical problems attendant upon sudden decreases in circulating fibrinogen have received extensive consideration in the medical literature. It is understood that the term "afibrinogenemia" signifies diminution in plasma concentration of this substance to values incompatible with normal clotting, rather than its complete disappearance from the circulation. The syndrome has been most frequently and thoroughly described in gravid women with certain specific complications of pregnancy, though it occurs also in carcinoma of the prostate,[1-5] in patients who have undergone pulmonary surgery,[6, 7] in carcinoma of the pancreas,[8] and in leukemia.[9] Some patients with afibrinogenemia also develop circulating fibrinolysins as well as deficiencies in other coagulation factors.

It is the purpose of this paper to present the second reported case in which both afibrinogenemia and amniotic fluid embolism are proved. The case here reported is unusual in that diffuse fibrin thrombosis was present at autopsy, in addition to clear-cut pathologic evidence of amniotic fluid embolism. In fact, the case is unique in that these fibrin thrombi involved both greater and lesser circulations. One previous case[10] may have demonstrated fibrin thrombi in the lesser circulation alone, but the microscopic description lacks detail. That such a situation might exist had been postulated, however, on clinical and theoretical grounds.[11]

Amniotic Fluid Embolism

The occasional presence of placental elements within pulmonary vessels of women who die during the puerperium was well known to European pathologists for many years.[12] Moreover, experimental amniotic fluid embolism was produced in animals as early as 1927.[13] The animals' reaction resembled the clinical picture in patients later described, and the author stated that pulmonary embolism was, in fact, the cause of death. He failed, however, to describe amniotic fluid elements in the lungs and did not suggest the possible clinical occurrence of the syndrome. The clinical significance of these earlier observations remained unappreciated, therefore, until 1941, when Steiner and Lushbaugh[14] described a syndrome of sudden dyspnea, cyanosis, and extreme shock occurring intra partum or immediately post partum. In their series of

*Aided by the Albert A. List, Frederick Machlin, and Hemophilia Foundation Research Funds.

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8 cases, labor was generally severe, occasionally tumultuous, and the infants, 3 living, 3 stillborn, and 2 undelivered, were larger than average. Several patients had clinical and pathologic findings consistent with cor pulmonale. The term "anaphylactoid shock," signifying symptoms of anaphylaxis in the absence of its immunological counterpart,[15, 16] was employed by Steiner and Lushbaugh to describe the clinical situation.

Since publication of the original report, 56 additional autopsy-proved cases have appeared in the British and American literature (to March, 1956).[10, 17-55] Scattered reports of presumptive cases with recovery have been published as well.[11, 56-58] Since a characteristic clinical course may occur without pathologic evidence of amniotic fluid embolism,[35, Case 2] some skepticism is justified in the absence of autopsy proof. In those presumptive cases with proved afibrinogenemia,[11, 58] where premature separation of the placenta and retention of a dead fetus have been ruled out, the evidence is perhaps stronger.

Of the 64 recorded cases, 8[14, Case 8, 17, Cases 1 and 2, 21, 23, Case 2, 28, 31, 35] presented autopsy lesions in addition to those of amniotic fluid embolism adequate to explain death. This is also true of the case to be presented.

Documented afibrinogenemia with autopsy-proved amnotic fluid embolism has been reported only once.[40] In a second case,[37] though fibrinogen levels were not directly measured, venous blood did not clot even after addition of thrombin, and in 3 others[10, 39, 51] in which no specific studies were performed, incoagulability of venous blood was noted. Each of these cases presented generalized bleeding presumably due to fibrinogen depletion. Blood studies in the first case referred to above, that of Ratnoff and Vosburgh,[40] revealed, in addition to fibrinogenopenia, slight hypoprothrombinemia, an antithrombin, and fibrinolysis.

The tendency to excessive uterine blood loss in amniotic fluid embolism has been alluded to before.[32] Excluding the cases where local factors could be held accountable for vaginal bleeding (9 cases in all), 15 of the remaining 55 had abnormal blood loss.[14, 19, 28, 29, 32, 33, 37, 38, 41, 47] Several authors[19, 24, 33, 52] mention absence of clots at autopsy. It is well known, however, that this may occur following sudden death[59, 60] due to a variety of causes.

The hypothesis has been offered that fibrinogen depletion as seen in amniotic embolism and abruptio placentae is a consequence of liberation of thromboplastic substances into the circulation.[11, 32, 61] Both amniotic fluid[62, 63] and decidual and placental tissue[64-66] possess thromboplastic activity, though the hemostatic effect of decidua is apparently many times greater than that of amniotic fluid.[67, 68] Schneider,[69] for reasons to be discussed below, believes that the clotting defect in amniotic fluid embolism is attendant upon the appearance of a heparin-like material in the circulating blood. He does, however, accept the thromboplastin-infusion theory in cases of afibrinogenemia complicating abruptio placentae, and has presented[70] an anatomic basis for the extraction of thromboplastin from decidual tissue by maternal blood, in the presence of a retroplacental hematoma. Similar anatomic studies by other workers[71, 72] have shown pathways by which amniotic fluid may also reach the maternal circulation. It seems apparent, then, that substances capable of initiating coagulation can enter the uterine venous system and thereafter be disseminated throughout the vascular tree.

If it is correct that defibrination is a result of intravascular coagulation, one might expect decreases in concentration of other factors involved in clotting. This is indeed so in those few cases of afibrinogenemia in which the coagulation mechanism was adequately studied. These patients may present decreases in platelets,[40, 73-76] prothrombin,[40, 77] and accelerator factors.[74, 78]

The fibrinogen level may drop with such great rapidity, both spontaneously and after therapeutic administration,[79, 80] as to indicate its destruction or consumption. Fibrinolysins, which are sometimes found, complicate the picture, since fibrinogen as well as fibrin may be destroyed by the enzyme.[81] It has been suggested[2] that fibrinolysins may act in vitro as well, after blood samples are drawn, so as to cause spuriously low fibrinogen readings. Whether fibrinolysins appear as a response to intravascular coagulation, or whether they develop primarily is difficult to decide, though they are by no means invariably found.

The pathologic lesions considered by most authors to represent intravascular coagulation consist of so-called "fibrin thrombi."[77, 82] These are fibrillar, eosinophilic, acellular (or almost so) masses found in small vessels in various organs. Whether they actually represent fibrin deposits cannot be stated with certainty, since similar deposits have been noted in a variety of circumstances[8, 82-85] where afibrinogenemia was not apparently present. (Of course, it is quite possible that this similarity in appearance does not indicate identity of either structure or pathogenesis.) Moreover, even in documented afibrinogenemia, disseminated fibrin thrombosis has been infrequently reported. It is conceivable that thrombi which do form may be dissolved by fibrinolysins. Animal experimentation has shown that venous thrombi induced by injection of sclerosing substances may disappear[86, 87] within 1 to 4 hours following intravenous administration of human plasmin (fibrinolysin). The fibrinolysins which develop in afibrinogenemia are usually exceedingly transient, and the possibility that they appear, though undetected, in many more cases than reports indicate, cannot be excluded.

As regards amniotic fluid embolism, fibrin thrombi have been reported in the lungs in two cases.[10, 34] One of these patients[10] had incoagulable blood and generalized bleeding during life. One of the original cases[14, Case 7] had moderate vaginal bleeding (500 c.c.) and "eclampsoid changes," not further described, at autopsy. Fibrin thrombi may be seen in eclampsia alone.[82] In a fourth case,[52] though excessive bleeding was absent, a definite clot was noted in an ankle vein isolated for a cut-down.

I have noted 3 additional reports of fibrin thrombosis in afibrinogenemia, 2[77, 78] in patients with abruptio placentae and one[8] in a patient with pancreatic carcinoma. An additional case of toxemia with abruptio[89] demonstrated extensive fibrin thrombosis at autopsy and excessive vaginal bleeding clinically, though a diagnosis of afibrinogenemia was not entertained.

Case Report

E. K., a 38-year-old gravida iii, para ii, was admitted to the obstetrical service of the Mount Sinai Hospital at 8:45 A.M. on Sept. 27, 1955, with an estimated date of confinement of Sept. 25, 1955. Her prenatal course was uncomplicated and past medical history negative. Her blood type was O, Rh positive. The membranes had ruptured at 5:00 A.M. on the day of admission.

There were no uterine contractions; the cervix was thick, the os admitting a fingertip. The blood pressure was 120/70, pulse 82. The fetal heart was audible in the left lower quadrant, rate 140, the vertex 2 cm. above the ischial spines. Over the next several hours, under stimulation of continuous intravenous Pitocin drip which was begun at 10:35 A.M., strong uterine contractions developed, the cervix dilating satisfactorily. At 2:25 P.M., moderate vaginal bleeding was noted, and venous blood did not clot.

Afibrinogenemia was suspected clinically and, though the cervix was 8 to 9 cm. dilated at this time, a 3,850 gram infant was delivered by midforceps rotation at 2:48 P.M. under nitrous oxide-cyclopropane anesthesia. The rim of the cervix was soft and pliable, and forceps were applied with ease. The infant did not breathe spontaneously, and the heart ceased beating 5 minutes post partum. The placenta separated spontaneously and

TABLE I

POSTPARTUM DAY	URINE			
	OUTPUT (C.C.)	SPECIFIC GRAVITY	ALBUMIN	SEDIMENT
0		1.010	Faint trace	5-6 WBC 1-2 RBC
1	180*	1.014	2 plus	Occasional WBC Many RBC
2	272		1 plus	4-8 WBC Many RBC
3	643	1.012	Faint trace	4-6 WBC 0-2 RBC
4	1,150	1.020	Trace	Many RBC
5	2,265			
6	2,680			
7	2,145	1.010	Trace	1-4 WBC Many RBC

*From 9:45 P.M. on day of delivery to 8:00 A.M. postpartum day 1. Remaining figures represent output to 8:00 A.M. of day indicated.

was manually extracted from the lower segment immediately after delivery; no retroplacental clot was present. During this period, large quantities of fluid blood issued per vaginam. The uterus and cervix were thoroughly explored, but no specific bleeding site was found. The estimated blood loss during delivery was 1,300 c.c.

The patient went into profound shock suddenly at 3:00 P.M., 12 minutes after delivery. At this time, petechial and purpuric hemorrhages were noted in the skin and about infusion sites. Shortly thereafter, whole blood, fibrinogen, and l-norepinephrine were started. The patient's blood pressure had to be maintained by pressor drugs for the next 47 hours. By 8:45 P.M. on the day of delivery, the patient had received 6,000 c.c. of bank blood, 8 Gm. of fibrinogen, 500 c.c. of dextran, and 2,000 c.c. of 5 per cent dextrose in water to which hydrocortisone and norepinephrine were added.

The postpartum course was complicated by oliguria and azotemia (Table I). Her mental state ranged from unresponsiveness to stupor, and a tracheotomy was necessary to facilitate suctioning of the lungs. On the fourth postpartum day, thrombophlebitis of the right leg developed, and on the eighth postpartum day, the patient had a convulsion followed by gasping respirations; she was pronounced dead 5 minutes later. Bleeding was not a clinical problem from the second postpartum day onward. Clinical and hematologic data are presented in Tables I to III.

Necropsy was performed 10 hours post mortem. There were petechiae and ecchymoses in the skin, subcutaneous tissues, and serous surfaces of the internal organs. Blood flowed freely from the left iliac vein, but with difficulty from the right. However, dissection of the superficial and deep veins of the right leg disclosed no evidence of thrombophlebitis.

The heart, which weighed 285 grams, showed slight hypertrophy of the right ventricle. Several white vegetations were present on the chordae of the tricuspid valve, and on the pulmonic valve. There was no destruction of underlying tissue, and on microscopic section the vegetations consisted only of fibrin and leukocytes.

There were moderate quantities of bloody sputum in the bronchial tree and recent emboli to the arteries of the right middle and lower lobes, as well as slight to moderate edema.

CLINICAL DATA

BLOOD									
HEMOGLOBIN	ERYTHROCYTES (MILLIONS)	HEMATOCRIT	PLATELETS	LEUKOCYTES	BUN (MG. %)	CO_2 MEQ./L.	Na MEQ./L.	K MEQ./L.	Cl MEQ./L.
13.2									
11.8	4.38	42	113,000	25,300					
13.0	4.78		48,000	21,600					
12.9	4.50		58,000	12,250					
		47.5			112	17.0	122	6.8	80
14.4				16,150					
13.5	4.77		36,000	18,300	172	17.6	127	6.9	86

TABLE II.* HEMATOLOGIC DATA

SPECIMEN	EFFECT OF ADDED THROMBIN	LYSIS	FIBRINOGEN LEVEL (MG. %)
For cross-match (9/27, 9 A.M.)	Normal clot†	None	
Immediately prior to delivery (9/27, 2:30 P.M.)	No clot		
After 1,750 c.c. blood; prior to fibrinogen‡	Small clot	3-5 minutes (complete)	144
After 4 Gm. fibrinogen	Small clot	Questionable	
After 8 Gm. fibrinogen	Good clot	None	224

*I am indebted to Dr. Martin C. Rosenthal for making available the data presented in Tables II and III.

†Thrombin not added to cross-match sample.

‡Taken through transfusion needle.

TABLE III. COAGULATION STUDIES, SEVENTH POSTPARTUM DAY

TEST	RESULT	COMMENT
Clotting time (3 tube)	5, 8, 10 minutes	Very poor clot
Clot retraction, 1 hour	1 plus	Many untrapped cells
24 hour	Not done	
Fibrinolysis, 1 hour	None	
24 hour	Not done	
Prothrombin time	17.0, 17.2 seconds	Small clot
10% prothrombin time	25.0 seconds	
Control prothrombin time	12.8, 13.0 seconds	
Control 10% prothrombin time	27.2, 27.0 seconds	
Serum prothrombin activity[131]	15.9, 15.2 seconds	
Thrombin time (0.1 c.c. thrombin [100 units per c.c.] plus 0.1 c.c. plasma)	14.5 seconds	
Control	6.0 seconds	
Labile factor[132]		
Clotting time, stored plasma	44.0 seconds	
Stored plus 0.1 c.c. patient's plasma	23.0, 23.2 seconds	
Stored plus 0.1 c.c. normal plasma	18.6, 19.0 seconds	
Fibrinogen[133]	197.9 mg. %	
Control fibrinogen	294.5 mg. %	
Platelets	40,000	

Several wedge-shaped hemorrhagic areas were present in the kidneys, but the intervening tissue appeared normal. Neither arterial nor venous occlusions were grossly visible. Scattered hemorrhage was present in the pelves, ureters, and bladder. The uterus measured 20 cm. in greatest dimension. Its wall was markedly hemorrhagic and thick and the cervix was hemorrhagic and necrotic. No uterine lacerations were found.

The pituitary presented a large area of necrosis centrally, surrounded by a narrow zone of congestion (Fig. 1).

The esophagus appeared acutely inflamed in its lower portion. Four shallow ulcerations were present in the duodenum and a large quantity of partially digested blood lay in the intestinal lumen.

The placenta was normal except for marginal insertion of the cord. No retroplacental clot or area of depression was present.

Microscopic Descriptions.—Multiple thromboses of small vessels were present in many organs. These stained deeply with eosin, phosphotungstic acid-hematoxylin, and periodic acid-Schiff reagent, and had a fibrillar structure. Specifically, they were present in the uterus, lung (Fig. 2, *A*), esophagus, kidney (Fig. 3), thyroid, duodenum, and myocardium (Fig. 2, *B*). Numerous emboli composed of epithelial squames were present in the lungs (Fig. 4), as well as congestion, hemorrhage, and the usual variety of granular thrombi.

Fig. 1.—Pituitary gland, showing central necrosis with peripheral zone of congestion and hemorrhage. An area of intact tissue remains.

The myocardium presented extensive necrosis with severe acute inflammation. No bacteria were demonstrable on Gram staining of direct smears and paraffin sections.

Hemorrhage, necrosis, and fibrin thrombosis were seen in the esophagus and duodenum.

In the kidney, the hemorrhagic areas seen grossly consisted of necrotic, congested renal tissue in which extensive fibrin thrombosis was present. No thrombosis of larger arteries was found in the necrotic areas, even in serial sections. Where the hemorrhage extended into the medulla, necrosis was present here as well. The remainder of the kidney revealed scattered foci of tubular necrosis with evidence of regeneration. Fibrin thrombi were seen in glomeruli at a distance from necrotic tissue, in the absence of necrosis.

The pituitary revealed extensive coagulation necrosis in which cell nuclei were not visible. Peripheral congestion was present, as well as a slight polymorphonuclear infiltration.

Extensive thrombosis, both granular and fibrinous, was present in the uterus and cervix. Occasional collections of epithelial squames were seen in myometrial vessels.

The remaining organs showed no microscopic abnormality.

Autopsy of the infant revealed massive aspiration of amniotic-sac contents, focal adrenal hemorrhage, generalized venous congestion and cyanosis, inspissated meconium in the proximal colon, and subarachnoid and intraventricular hemorrhage. The degree of hemorrhage was not unusual for intrapartum death due to asphyxia.

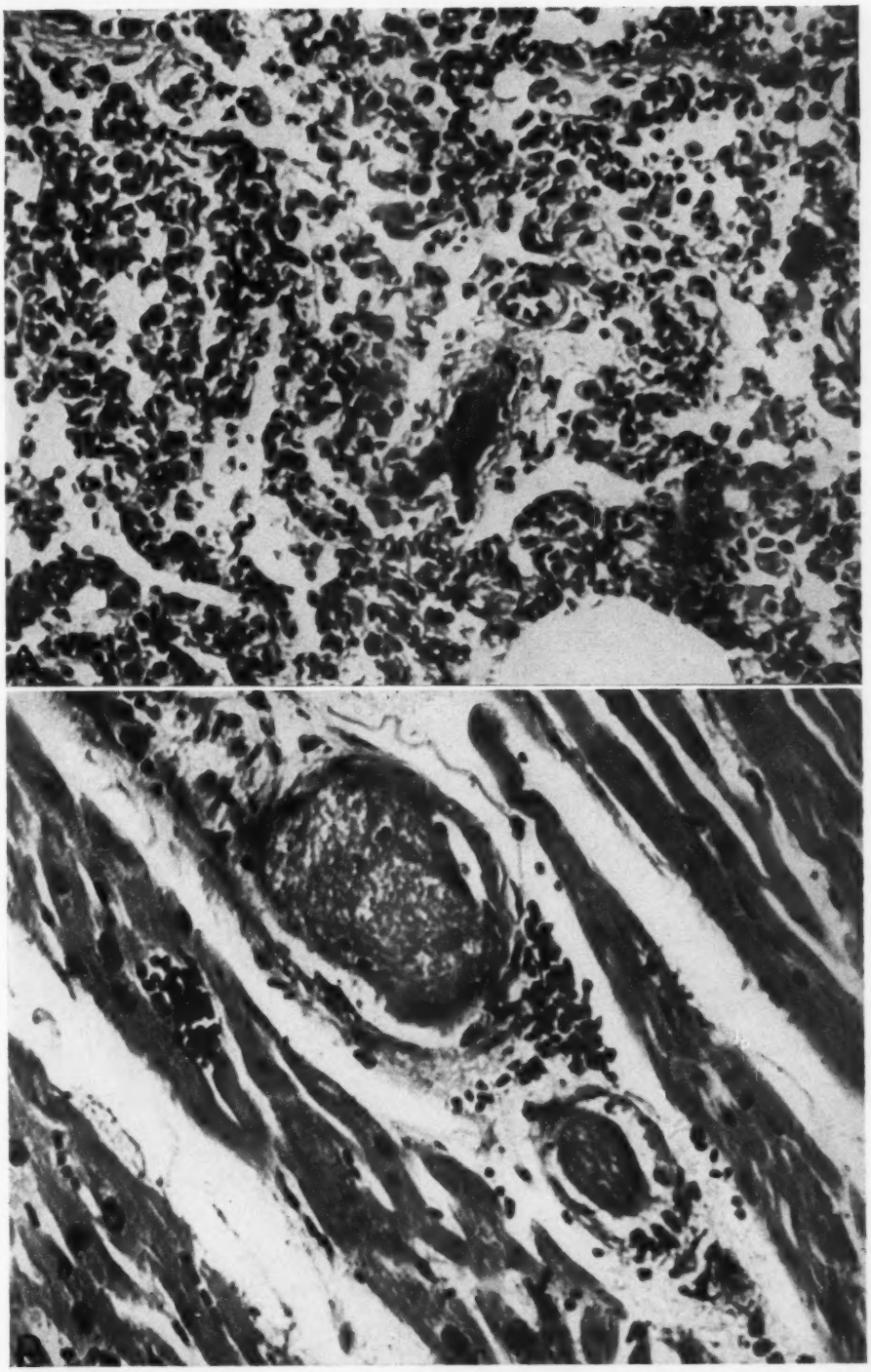

Fig. 2.—*A*, Lung, showing fibrin thrombus in pulmonary arteriole with surrounding congestion and hemorrhage. *B*, Myocardium. Two small vessels occluded by fibrin thrombi. (Hematoxylin and eosin. ×450.)

In summary, a multipara developed afibrinogenemia and shock after an episode of amniotic fluid embolism. The actual cause of death was considered to be pulmonary embolism. Though the degree of embolization would have been insufficient to cause death

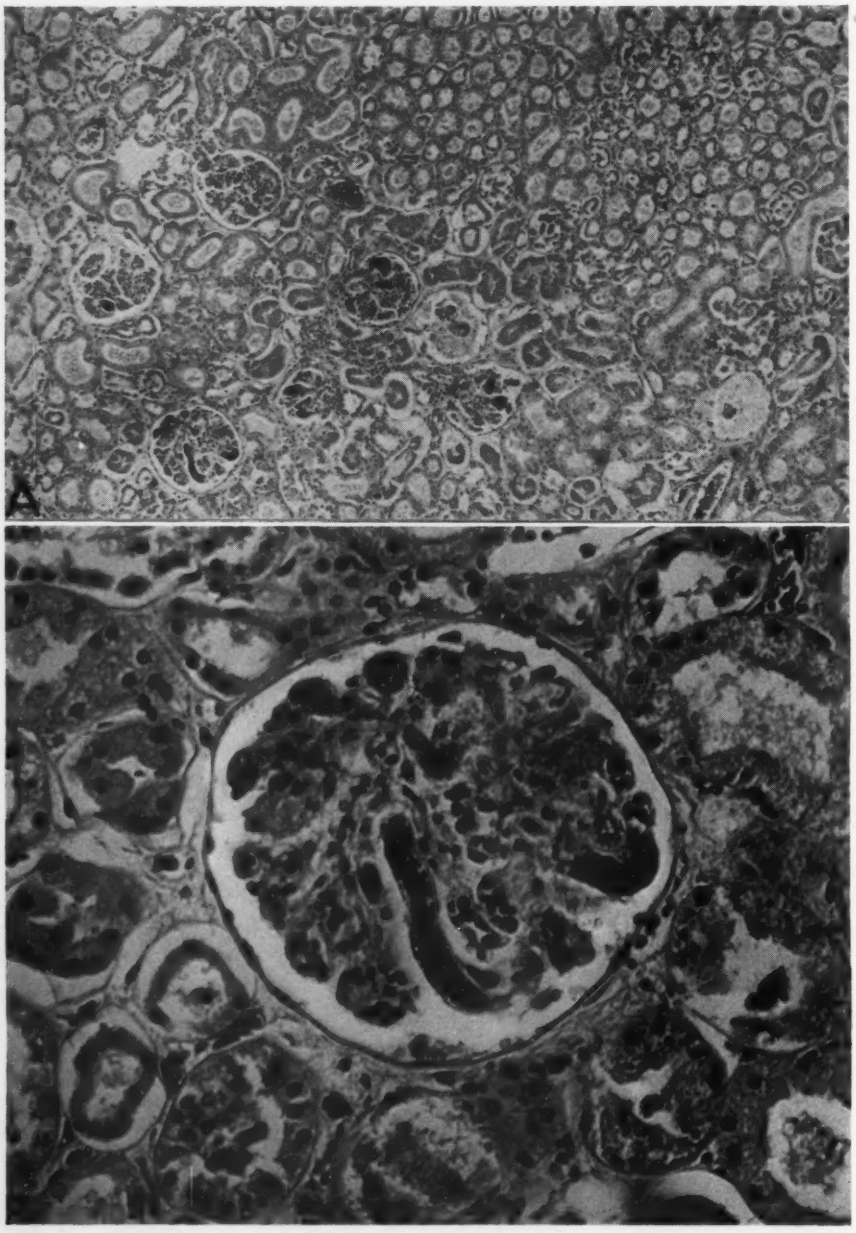

Fig. 3.—Kidney. *A*, Multiple glomeruli with capillary occlusion by fibrin thrombi. *B*, A single glomerulus showing fibrin thrombosis. Note absence of surrounding necrosis. (Hematoxylin and eosin. *A*, ×52; *B*, ×650.)

in most patients, in this case the final episode, in an individual who had already suffered severe shock and who sustained significant damage to a number of organs, was felt to constitute an adequate explanation.

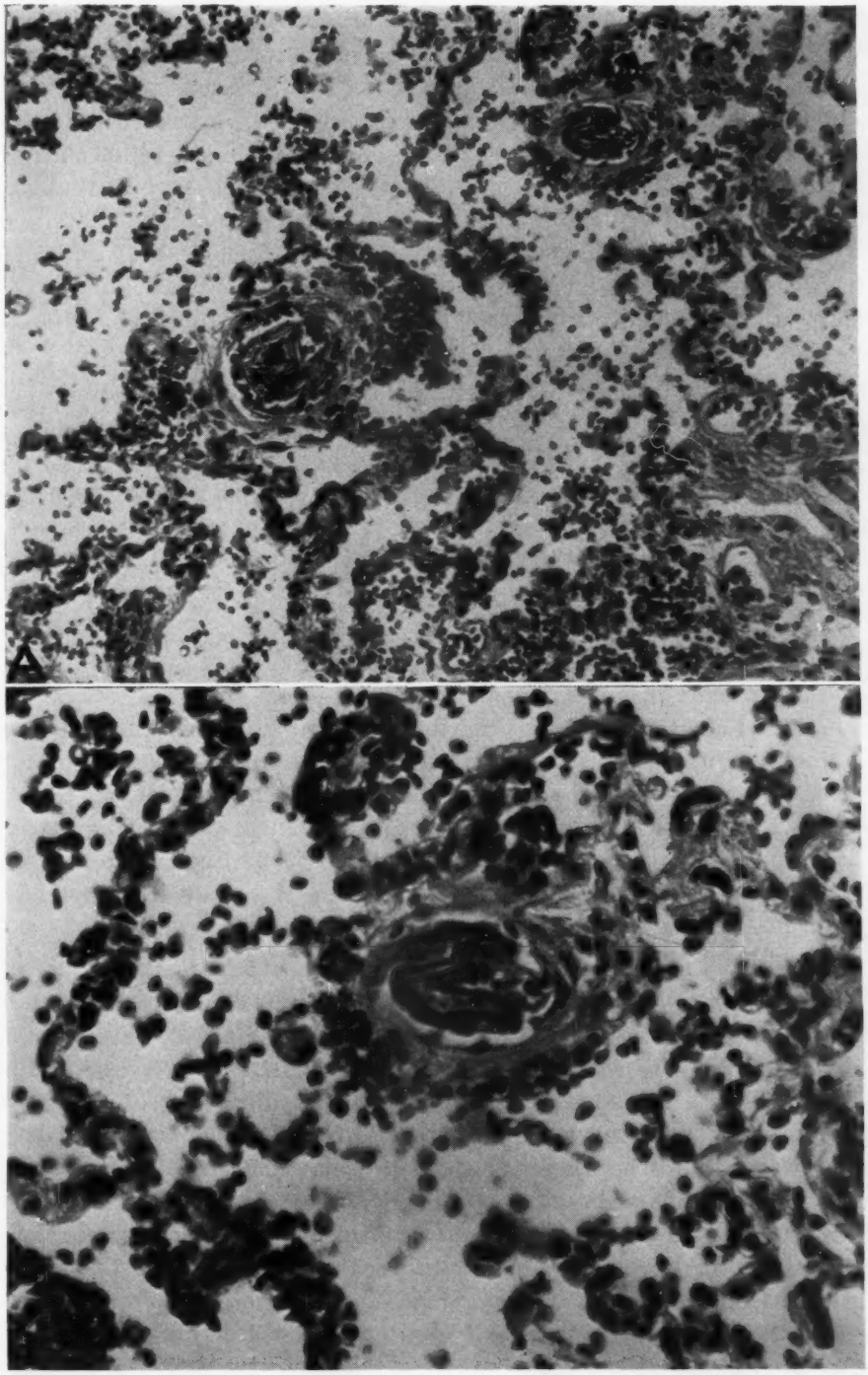

Fig. 4.—Epithelial squames in pulmonary arterioles. (Hematoxylin and eosin. *A*, ×200; *B*, ×750.)

Comment

Clinically, the patient's course was characteristic of amniotic fluid embolism. The vaginal bleeding which preceded delivery is presumed to have been caused by either a marginal separation or an extensive acute detachment, inasmuch as there was no pathologic evidence of a subacute or chronic form of premature separation. Table I shows that blood replacement was apparently sufficient to maintain adequate hemoglobin levels, though the measurements do not rule out acute anemia during and immediately after delivery. Continued thrombocytopenia, as illustrated here, may follow massive transfusion.[90] Blood chemistry determinations were not obtained until diuresis was established, but electrolyte and blood urea nitrogen values were characteristic of the diuretic phase of acute renal failure.[91]

The coagulation studies performed 7 days after the acute episode (Table III) disclose several abnormalities in the patient's clotting mechanism. Disordered prothrombin conversion is reflected by the abnormal prothrombin time and serum prothrombin activity; deficiency in labile factor was present as well. Despite a fibrinogen level considered adequate for hemostasis, the thrombin time was significantly prolonged. The suggestion has been made[92] that processing of fibrinogen may alter its biological activity in a manner not reflected by measurement of serum levels.

Pathologically, thrombi composed of dense, fibrillar, eosinophilic material were found in many organs. In the absence of other apparent causes for the severe myocardial necrosis, it was attributed to the fibrin thrombi. The polymorphonuclear infiltration in the myocardium was more extensive than that usually seen in necrosis without sepsis.[93] Though the presence of sepsis cannot be ruled out with absolute certainty, its presence would not change the essential significance of the clinical and pathologic findings. The possibility that fibrin thrombosis was the primary factor in the gastrointestinal ulcerations is an interesting speculation. In McKay's[8] case of carcinoma of the pancreas with afibrinogenemia, the same lesions were present in the rectum.

The pituitary lesion, in terms of Sheehan's[94] description, is between 4 and 12 days old; it presumably occurred, therefore, about the time of delivery. Fibrin thrombi, which Sheehan described in 10 of his 12 cases, were not present here.

The renal lesions deserve some comment. Grossly, they appeared as hemorrhagic infarcts, and the intervening tissue seemed normal. Microscopically, extensive fibrin thrombosis was present in glomerular capillaries and small arterioles. There were several scattered foci of proximal tubule necrosis alone, in which a thin layer of regenerating tubular epithelium covered the basement membrane, as described by Sheehan.[84] Aside from the lesions mentioned, the kidneys were microscopically normal. Nowhere were arterial occlusions found sufficient to explain the necrosis. The similarity of the necrotic portions to renal cortical necrosis[84, 95, 96] is striking, though lesions of the interlobular arteries usually described in this entity were not conspicuous here. One hesitates to implicate fibrin thromboses as the causative factor in the present

case, since these were present in intact portions of the kidney as well, and they may occur unassociated with renal necrosis of any kind.[83, 85, 97] It is suggested that a diagnosis of renal cortical necrosis made on the basis of a needle biopsy of the kidney[98] may be in error.

Experimental Work

For over half a century, experimental investigators have shown that there exists a connection between administration of tissue extracts and development of coagulation defects. Wooldridge,[99] in 1886, was apparently the first to publish such results. He injected extracts of thymus and testis into animals and produced extensive intravascular thrombosis with large doses. If smaller doses were given, thrombosis was less conspicuous, but venous blood was incoagulable. He referred to the latter phenomenon as the "negative phase" of coagulation, and noted that such a state protected the animal against ordinarily lethal doses of tissue extract. Several German investigators[100] had shown earlier that essentially the same results followed injection of intact leukocytes, but they did not work with extracts. The earliest experiments with placental extracts per se were apparently performed by Weichardt in 1902.[101] He produced convulsions, liver necrosis, and thrombosis of small vessels in liver and kidney by injecting extracts subcutaneously.

It seems unquestionable, in view of extensive confirmation of Wooldridge's work by many others,[64, 88, 102-114] that extracts of many tissues can produce coagulation defects by virtue of their thromboplastin content. Other sources of thromboplastin,[115] including amniotic fluid,[63] and even severe tissue trauma alone[116] may cause clotting aberrations.

There is considerable evidence, moreover, that the alterations in clotting time are due to fibrinogenopenia secondary to intravascular coagulation. Fibrinogen levels, measured directly, have been found to be reduced.[63, 67, 88, 113-115, 117] Shortly after injection of tissue extracts of various kinds, the coagulation time becomes sharply diminished for a short time (the "positive phase"), followed by a prolonged increase (the "negative phase").[63, 94, 106] Maximal resistance to subsequent injections occurs when the coagulation time is most prolonged.[94, 106, 112] Moreover, if the blood be rendered incoagulable by administration of heparin prior to injection of tissue extract, the toxic and hematologic effects ordinarily seen do not occur.[94, 106] Fulton and Page[112] showed that not only were refractory animals resistant to intravenous injections of thrombin, but that fibrinogen administration sufficient to raise fibrinogen concentrations to normal levels restored the animals' sensitivity to placental extract. The normal liver replaces fibrinogen with great rapidity[118]; the prolonged defect in clotting time may therefore represent loss of fibrinogen by destruction or continued intravascular fibrin deposition.

Pathologically, fibrin thrombosis has been demonstrated in experimental animals[88, 102, 110, 119-121] as well as in patients who die with afibrinogenemia.

Experimental studies do not offer invariable support to the thromboplastin-infusion, fibrinogen-depletion theory. The relationship between dosage and effect is difficult of interpretation, but some authors[114] believe that the

quantity of thromboplastic material required in experimental animals is so great as to cast doubt on the existence of a clinical counterpart in the human being. The refractory state may occur even though fibrinogen levels are not altered.[113] Schneider,[69] who feels that amniotic fluid embolism does not cause defibrination, has demonstrated the appearance of a heparin-like substance following experimental meconium embolism.[121] (He considers meconium embolism, rather than thromboplastin infusion, to be the experimental parallel to amniotic fluid embolism.) In these animals, blood does not clot in vitro after addition of thrombin even though fibrinogen levels are normal. (However, if amniotic fluid is centrifuged, the supernatant, in moderate dosage, can cause both fibrinogen depletion[63] and fibrin thrombosis.[119]) Hartmann and associates[113] also found an increased sensitivity to heparin, possibly indicating an endogenous release of this substance, after thromboplastin infusion in dogs. Another pertinent finding is that the prothrombin time may be normal during the negative phase,[111] a result inconsistent with severe fibrinopenia.

Previous authors[8, 97] have considered the possibility that the generalized Shwartzman reaction underlies the appearance of fibrin thrombi seen in various circumstances. Afibrinogenemia is not necessarily present.

The generalized Shwartzman reaction, first described by Apitz,[122] refers to development of renal cortical necrosis in experimental animals given two appropriately spaced intravenous injections of bacterial endotoxin. The earliest renal lesion, which appears about 4 hours after the second, or provoking, injection, is occlusion of the glomerular capillaries by dense, eosinophilic material.[123] Fibrin thrombosis of other organs is apparently absent.[123, 124] Parenthetically, it is of interest that the association of sepsis with fibrin thrombosis is not uncommon.[83, 85, 97]

A single injection, rather than two, is sufficient under three circumstances. Pretreatment with cortisone[125] or certain substances known to be concentrated in the reticuloendothelial system[126] are two of these. The third is pregnancy.[122] The association between bilateral cortical necrosis and pregnancy is, of course, well known.[84, 95]

More pertinent to the present discussion are several additional observations. Pretreatment with heparin prevents the reaction[127] for the duration of its anticoagulant effect, and the characteristic renal histopathology is minimal.[128] To my knowledge, studies of the coagulation mechanism in experimental animals have not been published, though Black-Schaffer and associates[129] reported increased bleeding times in every one of a series of animals in which cortical necrosis was produced and Apitz[122] regarded hemorrhage as a cardinal feature of the reaction. Moreover, more recent work supplies inferential evidence that fibrinogen is in some way altered after a single injection of endotoxin.[130]

While a large body of clinical and experimental work concerning afibrinogenemia, fibrin thrombosis, and cortical necrosis has appeared, the basic

mechanisms involved in their production remain unclear. The weight of evidence, however, despite occasional inconsistencies, seems to support the speculation that some relationship exists among them. More detailed studies of the coagulation mechanism in relevant experimental studies might well be productive in establishing a more positive connection.

Summary

1. A case of afibrinogenemia in pregnancy, with pathological evidence of amniotic fluid embolism and disseminated intravascular fibrin deposition, is presented.

2. The clinical and experimental literature on the subject is reviewed.

3. The presented case appears to offer evidence confirmatory of the theory that afibrinogenemia, at least in some cases, is a result of intravascular coagulation attendant upon release of thromboplastic material into the circulation.

I wish to thank Drs. Sadao Otani, A. F. Guttmacher, M. C. Rosenthal, L. R. Wasserman, Norman Herzig, and A. B. Gutman for their helpful suggestions during preparation of the manuscript.

Addendum.—Since the manuscript was submitted for publication, additional work bearing on the problem has come to our attention. Thomas and associates[134] have produced renal cortical necrosis by administration of a single dose of endotoxin in conjunction with certain synthetic acid polymers. In these animals, a fall in circulating fibrinogen can be demonstrated. A small series of rabbits given two injections of endotoxin alone, however, showed no change. Apparently, the renal changes develop much more rapidly when polymers are used, and these authors speculate that, following endotoxin alone, there is sufficient time for replacement of fibrinogen. Unfortunately, this publication escaped earlier notice.

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BREGMA PRESENTATION

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MOST of us were taught, as students, to recognize bregma presentation, and were warned that it was potentially abnormal. Yet search of the recent literature did not disclose any reference to this presentation, nor do most of the recent textbooks make any mention of it.

Martius[1] believes that brachycephaly plays a role in etiology and that if forceps delivery becomes necessary, no attempt at rotation should be made unless that rotation tends to occur spontaneously. Bumm,[2] referring to this entity as *Vorderhauptslage,* contended that it was apt to produce a difficult second stage of labor, and warned that forceps should not be used until after the frontal bone had passed under the symphysis. Barton Cooke Hirst[3] said of this presentation that it "resembles a brow. Descent is difficult and tedious. Serious injury to maternal soft parts is almost unavoidable."

Joseph B. DeLee[4] said it "closely resembles brow with which it is often confused. There are three possible outcomes—(1) late flexion and rotation anteriorly, (2) anterior rotation of forehead and further progress like a persistent occiput posterior, and (3) cessation of progress with head on the perineum."

J. Clifton Edgar[5] went into somewhat more detail and said, "authorities generally state that incomplete flexion resulting in a bregma situation is rare. My experience is that dystocia from this source is *most common.* I believe it to be one of the most important factors in the production of prolonged and tedious labors, either from tardiness in the rotation from a posterior to an anterior position due to the incomplete flexion or because the occipito-frontal circumference instead of the suboccipito-bregmatic is brought in relation to the periphery of the birth canal." He further says, "while some authorities consider that bregma demands a description of a special mechanism, I am accustomed to describe the condition as merely a departure from the mechanism of vertex presentation due to moderately incomplete flexion of the head. The mechanism differs from that of normal vertex presentation in that departure from the normal occurs by reason of the increased circumferences of the presenting part, and, further, the imperfect flexion brings the forehead down as far as the vertex, thus interfering with internal anterior rotation. It must be remembered that labor is not impossible in all cases of this condition, and that the several steps in the mechanism can be recognized as in other presentations. Should the partial extension be uncorrected, the mechanism is as follows: moulding is extensive by reason of the delay. Since the occipito-frontal diameter and circumference, and not the occipito-bregmatic diameter

and circumference, are brought in relation with the diameters and circumferences of the pelvic inlet, persistent bregma presentations undergo prolonged and characteristic moulding. Engagement and descent are slow by reason of the greater circumference involved; rotation of the head fails altogether because the vertex and forehead are equally influenced by the factors causing rotation, or is accomplished only with the greatest difficulty and much damage to the maternal soft parts. Labor often comes to a standstill by reason of the transverse position of the occipito-frontal diameter on the pelvic floor. The perineum begins to tear even before the head has reached it, on account of the great dilation of the upper vagina by the large cephalic diameters. The laceration becomes extensive, extending through the sphincter ani and even up the recto-vaginal septum. In expulsion of the head, the latter is born by propulsion and partial extension." He concludes by saying, "Immediate correction of the incomplete flexion should be performed either (1) by pushing the forehead up during uterine contraction, with two fingers in the vagina, at the same time making pressure upon the fundus; or (2) the whole hand may be introduced into the vagina and either the occiput drawn down or the forehead pushed up, counterpressure being at the same time made upon the podalic extremity of the fetus through the fundus, or upon the occiput through the lower uterine segment."

In our own personal experience, this type of presentation has seemed to be of more than just a little importance, and we, therefore, present the following résumé of our data.

Incidence

Our records show 61 examples in 6,405 primigravidas, or an incidence of about 1 per cent (Table I); 50 patients with bregma presentation in 12,433 multigravidas, an incidence of 0.4 per cent. There were therefore a total of 111 examples in 18,838 patients, or a general incidence of 0.6 per cent. We are quite certain that the incidence is considerably higher than this, as young house officers almost never make this diagnosis until it has been called to their attention at least once by a senior attending.

TABLE I. INCIDENCE

Bregma Presentation.—	
Primigravidas	61 in 6,405 = 1.0%
Multigravidas	50 in 12,433 = 0.4%
All patients	111 in 18,838 = 0.6%
Other Abnormal Presentations.—	
Brow	39
Face	26
Transverse	53
Compound	8
	126 in 18,838 = 0.7%

In this same group of patients, we encountered brow presentation 39 times, face 26 times, transverse 53 times, and compound 8 times, a total of 126 abnormal presentations, or an incidence of 0.7 per cent.

Etiology

The reason for the occurrence of this variant, midway between the usual occiput and the brow presentation is not apparent. Several factors may be involved (Table II). The higher incidence in primigravid patients has been noted. There were among these 111 cases, 4 examples of gross developmental anomalies, each of which might have been provocative of the unusual presentation. There was one example of Siamese twins, one two-headed monster, and two babies with hydrocephalus. Twin pregnancy was not of unusual frequency. There were two examples of the first twin presenting by the bregma, and 2 other examples of the second twin with this presentation were not included in the above figures. Cephalopelvic disproportion did not seem to be an important consideration. There was one example of a simple flat pelvis and one other patient in her first pregnancy who had a very large baby with a borderline pelvis.

TABLE II. ETIOLOGY

1. Primigravidity		1 %	
Multigravidity		0.4%	
2. Gross anomalies		4	
Siamese twins	1		
Two-headed monster	1		
Hydrocephalus	2		
3. First twin		2	
4. Contracted pelvis		2	
Simple flat	1		
Borderline	1		
5. Large baby (over 4,000 grams)			
Primigravidas		8 = 13% vs. 3.8%	in occiput presentation
Multigravidas		9 = 18% vs. 7.1%	in occiput presentation
6. Firm cervix			
Primigravidas		27 = 44% vs. 13 %	in occiput presentation
Multigravidas		10 = 20% vs. 3 %	in occiput presentation
7. Poor pains			
First stage:			
Primigravidas		36 = 59% vs. 25 %	in occiput presentation
Multigravidas		12 = 24% vs. 24.5%	in occiput presentation
Second stage:			
Primigravidas		29 = 52% vs. 50 %	in occiput presentation
Multigravidas		13 = 27% vs. 30 %	in occiput presentation

The size of the infant seemed to be of definite significance. Among the 61 primigravidas, there was one baby who weighed only 1,500 grams, but otherwise they ranged between 2,050 and 4,765 grams, with 8 of the 61 in excess of 4,000 grams. This is an incidence of 13 per cent versus only 3.8 per cent of large babies in the occiput presentation group. Similarly, among the multigravid patients, although there was one baby of 750 grams, and another of 1,525, the remainder ranged from 2,285 to 5,115 grams, with nine in excess of 4,000 grams. This 18 per cent is in considerable contrast to the 7.1 per cent of large babies among occiput presentations in our clinic.

Firmness of the cervix, whether result or cause, was a particularly frequent observation in this group of patients. Some degree of firmness was noted in 27 (44 per cent) of the primigravid patients, as compared to only 13 per cent in occiput presentation. Similarly, 10 (20 per cent) of the multigravid patients showed this finding, as compared to only 3 per cent in occiput presentation.

Poor uterine contractions in the first stage, as measured by our standards, were present in 59 per cent of the primigravid patients with bregma presentations, as compared to only 25 per cent of occiput presentations. This finding was not noted in the multigravid patients, in whom the percentage of poor uterine contractions (24 per cent) was the same as for other patients. The type of uterine contractions present in the second stage of labor was not different in this group from those in our clinic as a whole.

Study and restudy of these possible factors leaves us very uncertain as to whether herein may be found the real etiology of this presentation.

First Stage of Labor

The fact that six primigravidas and one multigravid patient had a first stage in excess of 24 hours at first suggests a very much higher incidence of prolonged first stage with this presentation (Table III). Careful review of the individual charts, however, showed that, in each instance, the prolongation could be explained entirely on the basis of the uterine contractions in relation to the resistance of the cervix, and that, therefore, the presentation had little or nothing to do with the prolongation. It is our present impression that this position does not adversely affect the first stage of labor to any considerable degree.

TABLE III. PROLONGED FIRST STAGE IN RELATION TO THE CONDITION OF THE CERVIX

	NORMAL CERVIX		FIRM CERVIX	
	NO.	DURATION	NO.	DURATION
Primigravidas.—				
Good contractions	10	Average 8 hours	3	Average 7 hours
Poor—improving	14	Average 16 hours	9	Average 24 hours
Always poor	10	Average 27 hours	13	Average 44 hours
Multigravidas.—				
Good contractions	16	Average 4.2 hours	4	Average 7 hours
Poor—improving	19	Average 9.0 hours	5	Average 13 hours
Always poor	5	Average 13.5 hours	1	Average 66 hours

Second Stage of Labor

There is a very marked difference in the second stage of labor between bregma and occiput presentations. In the former, labor is more prolonged, more difficult, and requires a much higher percentage of operative interference. Virtually all of the examples of so-called low transverse arrest in our clinic have occurred in patients with bregma presentation. This is in accord with the opinions of Hirst, DeLee, and Edgar.

Among the 29 primigravid patients in whom spontaneous rotation and flexion eventually took place, 24 were delivered spontaneously after an average second stage of 68 minutes (Table IV). This figure is very striking when compared with our experience with occiput presentation, where a second stage in excess of 1 hour occurs in less than 2 per cent of first labors. The 5 remaining patients in this group were delivered with low forceps after an average second stage of 150 minutes. Three other patients showed spontaneous flexion to an occiput, but no internal rotation. One of these was delivered spontaneously in 47 minutes, and the other 2 were delivered with low forceps after 88 minutes (average) in the second stage. Nine patients exhibited rotation but no flexion. Six of these were delivered spontaneously after an average of 42 minutes, and the other 3 were delivered with low forceps after an average of 35 minutes.

Sixteen of the patients exhibited neither rotation nor flexion (Table IV). Six were delivered spontaneously after an average of 45 minutes; 5 were delivered with low forceps after an average of 140 minutes; 4 were delivered with midforceps after an average of 98 minutes; one had a failed midforceps and was delivered by cesarean section after 137 minutes. The other 4 patients in the primigravid group were delivered as follows: Scanzoni rotation after Dührssen's incisions in 3 minutes; cesarean section at 4 cm. dilatation after 16 hours' labor on account of a Bandl's ring; Siamese twins with low forceps after 84 minutes; failed high forceps, not by a member of our regular staff, followed by intrapartum death and delivery by craniotomy after 50 minutes.

TABLE IV. METHOD OF DELIVERY IN SECOND STAGE—PRIMIGRAVIDAS

Spontaneous flexion and rotation	29		
Spontaneous delivery		24	Ave. 68 min. vs. 27 min. for occiput presentation
Low forceps		5	Ave. 150 min.
Flexion but no rotation	3		
Spontaneous		1	47 min.
Low forceps		2	88 min.
Rotation but no flexion	9		
Spontaneous		6	42 min.
Low forceps		3	35 min.
No flexion or rotation	16		
Spontaneous		6	45 min.
Low forceps		5	140 min.
Midforceps		4	98 min.
Failed midforceps		1	137 min. (cesarean section)
Scanzoni maneuver after Dührssen's incisions	1		
Cesarean section at 4 cm. dilatation	1		
Siamese twins (low forceps at 84 min.)	1		
Craniotomy after high forceps at 50 min.	1		

TABLE V. METHOD OF DELIVERY IN SECOND STAGE—MULTIGRAVIDAS

Spontaneous rotation and flexion	27		
Spontaneous		27	Ave. 17 min. vs. 11 min. for occiput presentation
Operative		0	
Flexion but no rotation (all spontaneous)	4		24 min.
Rotation but no flexion	9		
Spontaneous		8	Ave. 29 min.
Low forceps		1	Ave. 70 min.
No flexion or rotation	10		
Spontaneous		7	Ave. 18 min.
Low forceps		2	Ave. 22 min.
Hydrocephalus (dead) with craniotomy		1	10 min.

TABLE VI. AVERAGE DURATION OF THE SECOND STAGE FOR VARIOUS METHODS OF DELIVERY IN PRIMIGRAVIDAS

Spontaneous	37	Ave. 59 min.
Low forceps	15	Ave. 115 min.
Midforceps	4	Ave. 98 min.
Midforceps, including 1 failed	5	Ave. 106 min.
High forceps	1	50 min. (dead)
All others	3	With no mortality due to bregma presentation

The total incidence of forceps of 37 per cent in this group (Table VI) compares very unfavorably with our incidence of 14 per cent in occiput presentations. It should also be pointed out that the average duration of the second stage in primigravid patients with occiput presentations in our clinic is 27 minutes and that we do not believe in routine forceps, but employ them with very slight indications.

The data on the multigravid patients with bregma presentations are not nearly so striking (Table V). Twenty-seven of the 50 showed spontaneous rotation and flexion and were delivered spontaneously after an average of 17 minutes as compared with 11 minutes for our occiput presentations. Four others underwent spontaneous flexion but only partial or no internal rotation. All 4 were delivered spontaneously in an average of 24 minutes. Nine patients showed spontaneous rotation but no flexion, and 8 of these were delivered spontaneously after an average second stage of 29 minutes. In one patient of this group the second stage lasted 120 minutes and in this case we felt sure the prolonged second stage was due to the excessive weight of the baby (4,890 grams). The average time for the delivery of the other 7 was 29 minutes. An additional patient was delivered with low forceps at the end of 70 minutes.

In 10 instances there was neither rotation nor flexion. Seven of these patients were delivered spontaneously in an average of 18 minutes, and 2 were delivered with low forceps in an average of 22 minutes. The tenth patient in the group was one with a hydrocephalic dead baby that was delivered by craniotomy after 10 minutes. The total incidence of forceps in this group of 6 per cent is to be compared with an incidence of less than 1 per cent in our occiput presentations.

The modern-day use of episiotomy, usually more extensive when trouble from an overly large baby or a bregma presentation is expected, no doubt has reduced the second stage as described by Bumm, Hirst, DeLee, and Edgar. We cannot recommend too highly the use of episiotomy done as early and as deeply as seems necessary.

The same likelihood of poor uterine contractions noted in the first stage was also characteristic of the second stage. DeLee said that in the presence of good uterine contractions, this presentation might offer very little trouble. We agree. It is the combination of the adverse presentation and the associated tendency toward weak and infrequent uterine contractions that tends to produce "low transverse arrest." We repeat that this entity is seen by us almost exclusively with this presentation.

Third Stage of Labor

Among the primigravid patients, the average duration of the third stage of labor was 5.8 minutes as compared with 2.8 minutes for occiput presentations in our clinic. The average blood loss for this whole group was 265 c.c. Fifty of these patients had an average of 195 c.c. as compared with 185 c.c. for occiput positions. Eight of the others had an average of 680 c.c., strongly suggesting that the difficulties noted for the second stage of labor carry over to some extent into the third stage.

For the multigravid patients, the average duration of the third stage was 5.5 minutes, including one instance of 43 minutes in a patient with a uterus bicornis. Excluding this patient, the average for the whole group would be 4.7 minutes, while for the patients with occiput presentations the average was slightly over 2 minutes. Fifty of these patients had an average blood loss of 170 c.c., not greater than the over-all blood loss for our clinic. The patient

with the uterus bicornis and manual removal of the placenta lost 550 c.c. The tendency toward poor uterine contractions seemed to persist into the third stage.

Fetal Mortality and Morbidity

Among the primigravid patients, one baby that weighed 4,320 grams died intra partum as a result of failed high forceps. This death was clearly due to the operative procedure rather than to the condition present in the patient. Two other babies died post partum. One of these was the above noted Siamese twin, while the other died at the end of 12 hours with a pathological diagnosis of acute placentitis and fetal pneumonia.

Among the multigravid patients, there were 2 intrapartum deaths. One baby of 3,845 grams was the above noted two-headed monster. The other, 3,120 grams, was the above noted hydrocephalic infant. One other baby of 750 grams died one day after delivery.

If we could eliminate ill-chosen therapy, there should be no fetal mortality directly attributable to bregma presentation.

Since our fetal follow-up is not sufficiently complete, we can make no statement with reference to later fetal morbidity.

Maternal Mortality and Morbidity

There was no maternal mortality.

Among the primigravid patients, 2 developed pyelitis, one mastitis, one endometritis (the patient with the craniotomy), and 4 "one day fever" with no diagnosis. Among the multigravid patients, one had pyelocystitis, one septicemia (also the case of craniotomy), and 11 had "one day fever." The latter figure seems high, but we have no explanation for it.

Among the primigravid patients, 12 had minor injuries to the cervix. Four had lacerations of as much as 1 cm. and one had a deeper laceration. To these should be added the 2 instances of Dührssen's incisions. Among the multigravid patients, 3 had very minor cervical injuries. Three had lacerations up to 1 cm. in depth, and one a major cervical laceration. Serious vaginal and pelvic floor injury has not been particularly prominent in our experience, possibly because of early, and advisedly extensive, episiotomy.

Comment

We believe bregma presentation should be kept in mind, sought for, and carefully diagnosed when present. Whereas it should produce no fetal losses, and little or no maternal morbidity, it can result in ill-judged clinical management and perhaps, thereby, lead to fetal mortality and maternal morbidity.

A definitely longer second stage can be expected. This longer second stage need not be particularly deleterious and attempts to shorten that longer second stage may be ill advised.

We are, however, not quite convinced that we should go back to Bumm's recommendation of not using forceps until the frontal bone emerges under the symphysis. We are also convinced that rather early attempts at flexion are justified but we must, nevertheless, point out that this procedure is often unsuccessful. One must, we feel, train himself to flex the head properly on, or just above, the pelvic floor. We do not feel, with Martius, that forceps

rotation is a necessary part of the delivery procedure. In fact it may well be that delivery, because of the unusual head molding, can be better effected by deep episiotomy and delivery without rotation.

Conclusion

Bregma presentation is an important variant midway between the abnormal brow and the very normal occiput presentation, markedly different from either so far as the course of labor is concerned. It should be carefully and thoroughly described in our modern textbooks.

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PREGNANCY ASSOCIATED WITH SEVERE ANGULAR DEFORMITIES OF THE SPINE

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UNFORTUNATE indeed are those women with severe angular deformities of the spine who become pregnant. This applies in general to all women in this group. It applies particularly, however, to those in whom the lesion involves the dorsal as opposed to the lumbar spine. When the latter is principally affected, the problem is usually one primarily of obstetrics. On the other hand, in that group of women in whom the dorsal spine is the part primarily involved, although the pelvis itself is less frequently distorted, there is the constant added threat of one or more serious associated medical problems. It has been found that the thoracic organs in these patients are much more frequently and profoundly affected. This is especially true in those in whom the deforming lesion has occurred before the age of maturity. According to Chapman, Dill, and Graybill,[1] there is an actual lack of development on the part of the lung tissue in this group of patients. As a result, the vital capacity of such a patient is profoundly affected. This, in turn, creates an increased burden on the right heart in such an individual of sufficient severity as frequently to shorten her life.

As a result of these changes which profoundly affect their cardiac and pulmonary function, the patients of this group often present a serious medical as well as an obstetrical problem. They do not tolerate anything which may place a further burden upon these thoracic organs. Hence, they do not react favorably to general anesthesia of any kind. Depressant drugs, such as morphine, even in small doses, may be fatal to such a patient, as shown by Fearl[2] and others. They further respond poorly to any extensive surgical procedure.

For the same reasons, Eastman[3] concluded that these patients in general are poor obstetrical risks. Because of the lack of accommodation of the rib cage which is fixed and the further burden on the already handicapped heart and lungs, he believes pregnancy and delivery in such patients may be extremely serious and even fatal. The following case report clearly confirms this view.

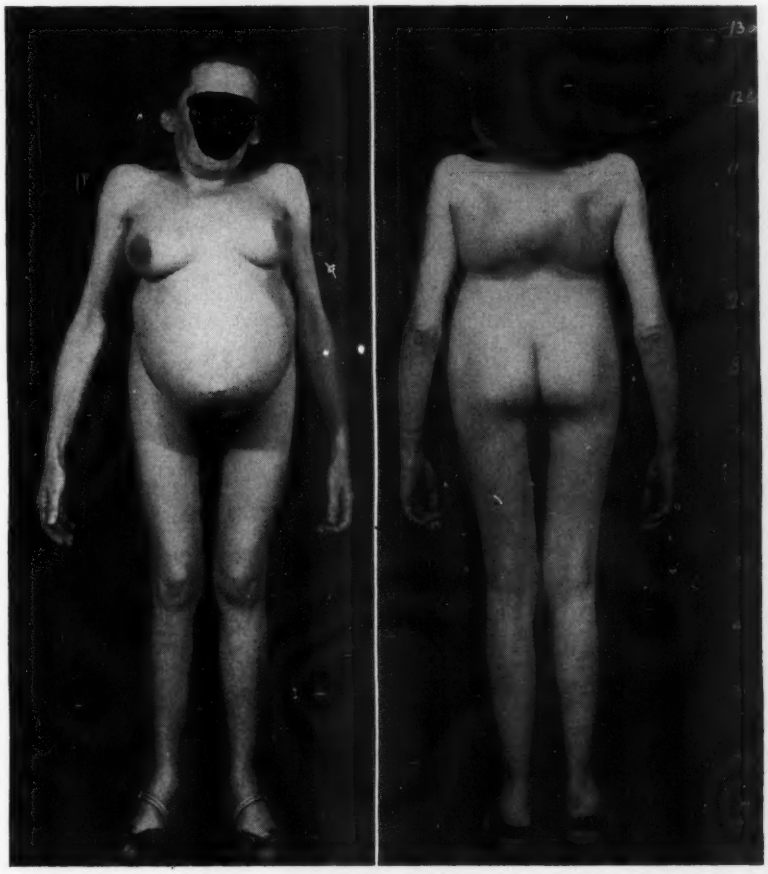
Case Report

Mrs. C. O., a 38-year-old primipara, was first seen in consultation Feb. 13, 1954. She had previously reported to her family physician because of amenorrhea, abdominal enlargement, and increased size and weight of the breasts. These suggested early pregnancy which was confirmed by laboratory tests.

As a result of the increasing discomfort due to the abdominal enlargement associated with more marked respiratory distress, the patient was hospitalized. It was at this time that I first saw her because of the question of interruption of the pregnancy. Because

she had been married 8 years with no previous pregnancies and because of the extreme insistence on her part—and that of her husband—on having a baby, it was decided to allow her to continue her pregnancy under close supervision. At that time, the period of gestation appeared to be about 18 or 19 weeks.

Aside from the abdomen which was already becoming markedly pendulous, physical examination showed a severe angular deformity of the dorsal spine. This was substantiated by x-ray which showed the gibbus most marked on the right. Râles were found at both bases. There was also thought to be some evidence of cardiac enlargement.



A. *B.*

Fig. 1.—*A*, Anterior view of patient. *B*, Posterior view, showing the gibbus involving the dorsal spine primarily and the shortened stature.

Her past history was essentially negative except for a severe fall and spinal injury at the age of 4 years, resulting in the scoliokyphosis now present.

Aside from very little weight gain and no demonstrable edema, the prenatal course became increasingly difficult to manage. With the rapid enlargement of the abdomen, there was progressive generalized discomfort and especially increased difficulty in breathing. This even reached the point where early interference with the pregnancy was again considered as a definite possibility. However, she was allowed to carry to about the thirty-ninth week of gestation. At that time, due to the breech presentation, along with the acute anteflexion of the uterus as shown in the x-ray pictures, cesarean section was deemed advisable, although her pelvic measurements were well within normal limits. This method of delivery was further favored because of the need for immediate relief of the chest symptoms.

At operation the abdominal wall was incised in the midline, with the use only of 1 per cent Novocain infiltration. Because of the acute anteflexion of the uterus and the limited abdominal space, it was found that the lower uterine segment could be reached only with the greatest difficulty. Hence the baby was delivered through a midline classical approach in the fundus. Small amounts of intravenous Pentothal were employed in support of the Novocain during this intra-abdominal manipulation. The patient, however, responded poorly to the anesthesia throughout the entire procedure.

Fig. 2.—Showing the markedly pendulous abdomen and diminished chest cage.

The patient's postpartum course in the hospital was surprisingly uneventful. Against her physician's advice, she was allowed to leave the hospital on the fifth postoperative day in what appeared to be remarkably good condition. No cardiac stimulant at this time was deemed necessary. Her condition remained satisfactory up until the evening of the 13th postpartum day. At that time, with very little warning, she lapsed into unconsciousness and died in a manner similar to that described as a pulmonocardiac failure, so common in this group of patients. Unfortunately, no autopsy was obtained.

Comment

Fortunately, the combination of pregnancy and a severe angular deformity of the spine is not commonly found in the same patient. As early as 1896, according to Williams, Klein[4] placed the incidence as roughly 1 in 6,000 deliveries, although he felt it was more frequent. Fearl, however, in 1951,

placed it at 1 in approximately 12,000. This decline in frequency probably results from the fact that such etiological factors as caries due to rickets, tuberculosis, poliomyelitis, and other infectious diseases are resulting in fewer such spinal deformities as time goes on. Also, the efforts of the orthopedic surgeons in the presence of kyphosis, scoliosis, and kyphoscoliosis are beginning to make very definite headway.

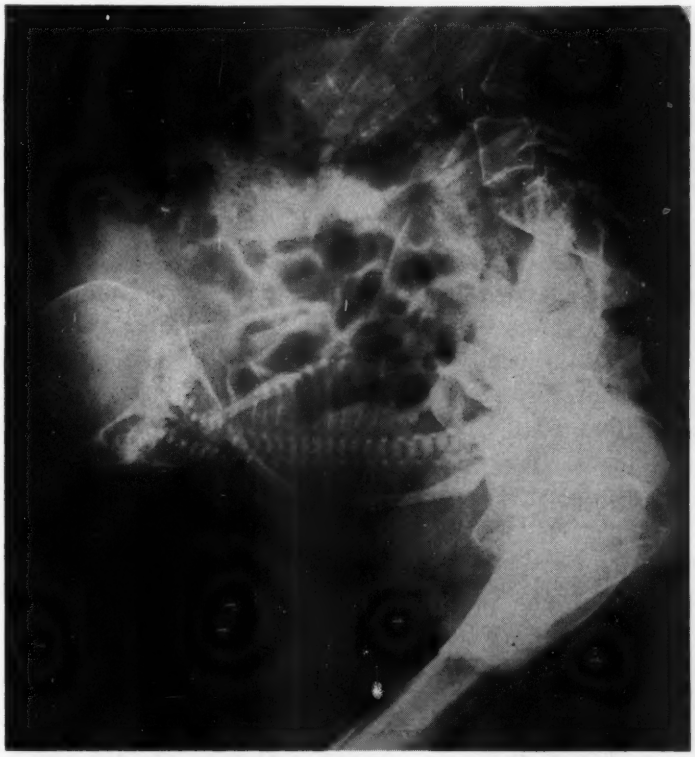


Fig. 3.—Lateral x-ray showing the acute anteflexion of the uterus and its contents at 32-34 weeks' gestation.

In spite of all these advances, however, it must be assumed that for a long time to come there will be an occasional woman with such a deformity as the result of hereditary and/or congenital factors or trauma who will become pregnant. For this reason, it is extremely important that the trained obstetrician who sees a patient in this group not only be entirely familiar with the over-all picture of the pregnancy but he should also be cognizant of any and all of these associated medical complications. Finally, he should be in a position to understand fully the mental reactions associated with such a twisted and deformed body in which pregnancy occurs.

Because the life of the hunchback is so frequently handicapped or already shortened, the question of the advisability of allowing a pregnancy, first, to occur and, second, to continue in such a patient arises at times, as it did in the patient's case herein presented. For this reason alone, one's knowledge must be complete before proper evaluation and mature judgment can be

established. As an example, Fearl, with others, points out that the vital capacity in these patients assumes a new and far greater importance under such circumstances than it does in the normal pregnant woman. The simple ability of such a patient to accommodate by chest expansion, especially on lying down, is another determining factor of equal value in arriving at a wise decision. Finally, age, which in the normal pregnant woman has comparatively little importance, may become the deciding argument against allowing the pregnancy to continue. It has been shown that such a patient, when over 30 years of age, becomes a markedly increased risk.

As late as 1951, Hanley, in his discussion of the presentation by Fearl on this subject, called attention to the marked lack of understanding in the handling of patients in this group. He especially stressed the ignorance of the obstetrical profession in general as to the associated complications which may occur in the female hunchback who becomes pregnant.

This general lack of knowledge has apparently resulted from the fact that all standard obstetrical textbooks of the past and a majority of those used today, as well as most of the medical literature in general, discuss only the purely obstetrical problems which may occur when various parts of the spine in the pregnant woman are involved by scoliosis, kyphosis, or a combination of the two. Up until recently, with rare exception, none of these textbooks and few of the articles in English on the subject considered even the physical complications which are peculiar to this group. Few if any included consideration of the accentuated emotional side of pregnancies in these physically handicapped individuals.

It is because of the paucity of such specific information to date that this particular case history was felt to be an excellent example of some of these points which require unusual emphasis.

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RECTAL INJURIES DURING VAGINAL DELIVERY

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MANY experienced obstetricians have had an occasional case of laceration of the rectum with an intact rectal sphincter following a vaginal delivery. This complication is relatively rare, but almost nothing appears in the literature relative to its prophylaxis or treatment. We have noted this accident on several occasions in both our private cases and on service patients. Other obstetricians when questioned reported that they also have had this difficulty. It was decided that this problem certainly deserved closer scrutiny.

On reviewing our cases and those made available to us by other physicians, one fact was outstanding. All cases had an episiotomy, either midline or mediolateral. Most of the deliveries were comparatively simple, and when the episiotomy was inspected before repair, the obstetrician was surprised to find a hole going through from the vagina into the rectum with an intact rectal sphincter. The rectal wall was intact from the anal margin to the point of the injury, a distance of 2 to 5 cm. This we called a "button hole laceration." It occurred 8 times in 7,500 deliveries.

This laceration of the rectum was never noted when perineotomy was not done. With lacerations or extension of small episiotomies spontaneously, this lesion has never been seen. We are aware that a "button hole" may result without any operative interference if the rectovaginal septum is involved in lymphogranulomas, etc., but in all the cases herein reported there were no pathological conditions of the rectum, deliveries were deliberate, and there were unusual extensions of the perineal incisions. All of these patients had rectal examinations during labor and the rectum and perineal tissues showed no abnormality.

The most logical approach to the problem was to follow the course of the lower rectum during an actual delivery. A finger was inserted into the rectum and kept there throughout a number of deliveries, both spontaneous and forceps. The maneuver demonstrated that some women had excessively thin rectovaginal septa (congenital or posttraumatic). As the head began to descend to the pelvic floor, it pushed the rectum forward in front of it and caused it to protrude like an inflated ball into the vaginal introitus (Fig. 1). With crowning, the rectum was flattened, forced posterior and upward, and consequently pushed out of harm's way. It was concluded, therefore, that there is a greater possibility of producing a "button hole" injury if the episiotomy is performed before crowning (Fig. 2).

If it is deemed advisable to do an early perineotomy, one should protect the rectum by putting two fingers into the vagina in an inverted V fashion and pushing posteriorly and inferiorly, thus putting the perineum under tension and imitating the action of the infant's head.

Other factors seemed to contribute to the occurrence of this accident. On several occasions a resident was observed making a small episiotomy, and then, with further descent of the head, enlargement of the original incision was necessary. A second incision was attempted into the vagina and into the depths of the episiotomy in a rather blind manner with scissors. When the delivery was completed and the area inspected, a "button hole" was found. It is now advocated that an adequate incision be performed at the first attempt. If further extension is desired, the incision is made under direct vision only in the vaginal mucosa or skin and subcutaneous tissue. If deeper structures must be cut, a guiding finger should be put into the rectum.

Fig. 1.—The lower rectum is shown being pushed forward in front of the advancing head before crowning.

Another element in the production of this lesion is pointed scissors. It is very easy to perforate the rectum even with blunt scissors because the rectal wall is under tension and it is quite likely to be caught between the two pinching, closing blades. Because of this, many obstetricians prefer to use a knife in order to do away with the tendency of scissors to grab the rectum. If, however, scissors are used, they must be blunt with rounded ends.

There is no definitive treatment given in any standard text or in the current literature for a "button hole" injury to the rectum. Although some physicians advocate cutting through the sphincter and converting this condition into a fourth-degree laceration, we have rejected this approach because cutting both the external and internal rectal sphincters at the same time increases the possibility of rectal incontinence should healing not occur, a rare but possible complication. It is also our feeling that no matter how meticulous one is in repairing a sphincter, it is never quite as efficient as it was initially. Further,

it does not seem logical to us to convert a small hole into a much larger one. It is our experience that a simple closure of the rent in the rectum is all that is needed. All of the cases so treated healed promptly, recovery was uneventful, and no fistulas occurred. While we have a healthy respect for all injuries of the genital tract, as obstetricians we have learned that almost all lacerations in this area will heal promptly and completely if they are recognized and repaired at once.

Fig. 2.—With crowning the rectum is compressed and forced posteriorly, accompanied by elongation and stretching of the perineum.

Description of Repair

A finger is inserted into the rectum. This clearly outlines the laceration and shows the exact boundaries. Usually it is from 1 to 2 cm. in length. Thin vaginal retractors are inserted into the vagina and pulled laterally to aid exposure. No. 3-0 interrupted chromic sutures are inserted into the perirectal fascia about 0.5 cm. apart (Fig. 3, *A*). The rectal mucosa is not entered. The first suture is just above the apex of the laceration, and the last just below the lower angle.

After completion of the first row, the operator's gloves are changed and a second row of similar sutures is inserted to reinforce the injured rectum and prevent leakage (Fig. 3, *B*). The episiotomy is then closed in the usual fashion, but interrupted sutures should be used. Care should also be taken to put a layer of perivaginal tissue between the vaginal mucosa and the rectal area if this is available. There is a general tendency to use too much catgut. Unfortunately, this does not give added insurance, but contributes to breakdown of the repair because of tissue strangulation.

Postpartum Care

No mineral oil was permitted. It was felt that it had a tendency to seep through the suture line. Combiotic (2 c.c.) was given twice daily for five days.

The patient was permitted out of bed on the second postpartum day and was not restricted in any way. She ate a regular diet. On the fourth and fifth postpartum evenings, the patient was given 1 ounce of milk of magnesia if her bowels had not already moved spontaneously. Most patients did not need this because with an intact sphincter they did not have much pain and their bowels moved easily by the third day. If necessary, a small enema consisting of 2 ounces of Phospho-soda, 1 ounce of hydrogen peroxide, 1 ounce of glycerine, and 2 ounces of water was given on the sixth morning. Large enemas were avoided.

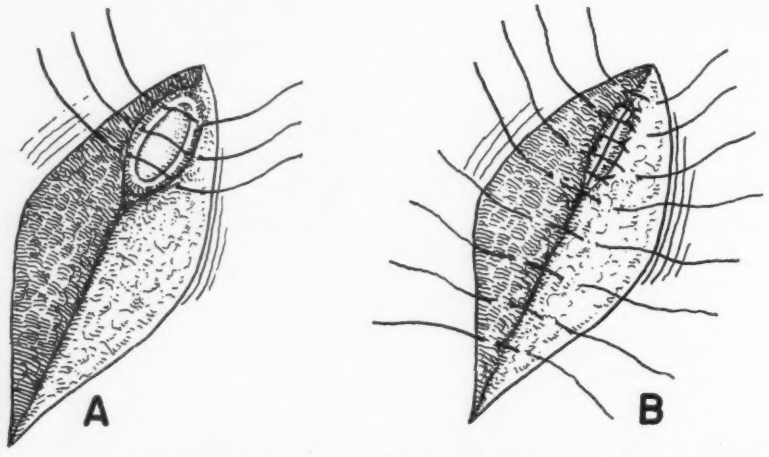

Fig. 3.—*A*, Closure of defect in rectum with interrupted sutures in the perirectal fascia. *B*, Second layer of interrupted sutures.

Summary

1. A traumatic injury during vaginal delivery is described which creates an opening between the vagina and rectum with an intact rectal sphincter. This is called a "button hole injury."

2. The course of the normal rectum has been followed throughout complete delivery, and it is postulated that this condition is caused by early episiotomy before the crowning head pushes the rectum back. Other causes are blind cutting to extend an inadequate incision and the use of pointed scissors.

3. It is suggested that if early episiotomy is desired, it is desirable to use the fingers of the opposite hand as an inverted V and pull down on the perineum. This acts as a substitute for the perineal mechanism normally produced by the baby's head.

4. If one is aware of the possibility of this injury, and makes the diagnosis, the repair is simple. Healing and end results are excellent.

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THE CLINICAL ISSUES OF POSTPARTUM PSYCHOPATHOLOGICAL REACTIONS*

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IT WAS almost exactly twenty-nine years ago that I offered my first communication on "Malignant Psychoses Related to Childbirth."[1] The paper was presented before the New York Obstetrical Society on May 10, 1927; that is to say, before the official advent of what is termed today psychosomatic medicine.

What puzzled me then and, I must admit, still puzzles me now is the question of what relationship these psychopathological reactions bear to childbirth, and what are the clinical criteria that would enable us to foresee, if not predict accurately, serious psychopathological sequelae of childbirth. At the time these studies were started, the serious psychological complications of childbirth were traditionally called puerperal psychoses, and during the three-quarters of a century before then these psychoses were considered as caused by the pregnancy itself, or the puerperium, or lactation. The psychosis itself was traditionally related to the period during which it became clinically evident.

As these studies proceeded it became more and more clear that the psychoses in question were not separate entities; that from the standpoint of formal clinical psychiatry these psychoses belonged, generally speaking, to the two large groups of schizophrenias and depressions; that they were not related particularly to pregnancy but to the act of parturition. In other words, pregnancies that are marked by psychological tensions, severe moods, and anxieties are not really abnormal pregnancies, and so-called common sense to the contrary, the so-called psychologically uneventful, serene, and "sunny" pregnancies are apt to be harbingers of severe and even malignant postpartum reactions. This does not mean that all psychologically uneventful pregnancies are forerunners of postpartum psychoses, but they frequently may be; whereas the so-called psychologically stormy pregnancies seldom are such forerunners.

The puzzle remained unsolved, however, apparently because the answer was to be found in the field of psychopathology, and psychopathology seemed rather unclear on the subject. Unless one decided to cling to the untested and unproved ad hoc quasi endocrinological hypothesis, it seemed difficult if not impossible to understand why motherhood—the most natural of all states—should prove such a disastrous condition for so many women. The answer had to be sought in the deeper layers of women's psychology, in those psychological structures which as a rule remain unconscious. Following this trend, it soon became

*Presented at a Joint Meeting of the Sections on Obstetrics and Gynecology, Neurology and Psychiatry of the New York Academy of Medicine on April 24, 1956.

evident that it was the mother's reaction to the act of childbirth itself that had something to do with her unconscious attitude toward the newborn child. Yet this bit of evidence can be observed directly only in certain cases—namely, in those women who become acutely depressed immediately following childbirth and who, some time within the first hours post partum, have suicidal and at times also infanticidal ideas and impulses. Unfortunately, we learn all this after the attack becomes pronounced and not before; moreover, as I have said, the phenomenon usually becomes apparent only in cases of acute depressions, and not in the schizophrenic reactions which represent approximately one-half of postpartum psychoses.

I may add here, parenthetically, that keeping the baby away from the mother during the first 24 or 48 hours post partum thus serves not only preventive hygienic purposes, but also psychological ones. It would be a rather risky practice to leave any mother alone with her baby 24 or 48 hours post partum. This measure is important not only for primiparas but especially in the cases of multiparas, because the incidence of postpartum psychoses is much greater among multiparas.

This parenthetic remark carries with it some emphasis if we bear in mind the practice which has been established in certain obstetrical circles the world over of having the baby with the mother all the time—from the moment of childbirth. Unless careful attention is paid to the mother's reactions, such proximity of the child might prove injurious in that it would serve as an added and tangible precipitating factor of a postpartum psychopathological reaction in certain women. The candidate for such a reaction might escape the psychosis, or its severity, if the child were not right with her when she regained consciousness. During the first 24 or 48 hours, a mother could be prepared psychologically for her first real meeting with her child.

Without going into the details of the findings yielded by the first studies of postpartum psychoses, I may say this: the negative findings by far outweighed the positive ones. Thus it was found that on the purely clinical level the obstetrician could not predict which woman might and which might not develop a postpartum psychosis. The superficial psychological picture may not offer any lead as to the probability of a postpartum psychosis. As a matter of fact, it may mislead: thus, the conscious wish to become pregnant is no guarantee at all that the given woman will enter motherhood unscathed from the psychiatric point of view; on the other hand, the conscious desire not to have a child is no indication that postpartum complications are in the offing. Many women attain physically and mentally healthy motherhood following a considerable period of preliminary fear and active avoidance of pregnancy. The absence of any history of previous psychotic attack is no guarantee against a postpartum psychosis; as a matter of fact, as it was already alluded to, what is rather characteristic of a postpartum psychosis is that it is always, or almost always, the first psychotic attack in the life history of the woman in question. The fact that a woman has already had a child or two without any psychological complications is again no sign that there is smooth sailing ahead, for the majority of postpartum psychoses occur in multiparas.

The variety of paradoxical findings in connection with postpartum psychopathology leaves the obstetrician very much in the dark as to the anamnestic approach and prognostic criteria he must use in order to be able to work in an atmosphere of what might be called psychiatric certainty. The psychiatrist can seldom be of any direct help in such cases, because the average woman will not look with great favor on the suggestion of the obstetrician that a psychiatric consultation might be desirable, "for no reason whatsoever" so to speak. The obstetrician too would hardly feel convinced that he needed a psychiatrist's help—at any rate not until such help becomes clinically unavoidable, which is usually late as far as taking preventive measures is concerned.

There is therefore little doubt that the issue belongs to the domain of prenatal care, and that it is the obstetrician who must be equipped with some sort of preliminary tools which he could use with a certain degree of clinical independence as the pregnancy progresses. I must say at once that, when I speak of the psychiatric tools which must be at the disposal of the obstetrician, I do not have in mind the rather loosely knit and even more loosely conceived network of so-called psychosomatic considerations. I must be definite on this point, because I am unable to find any theoretical and still less clinical basis for this hyphenated point of view, at least as far as postpartum psychoses are concerned. As I have already said, the stormiest pregnancies usually end very happily as far as both mother and child are concerned. I have had experience with the most severe forms of difficult pregnancies, during which asthmatic attacks, extreme and almost dehydrating salivation, and migraines failed to be of any moment in the happy outcome of the pregnancies involved.

When I speak of the psychiatric tools of the obstetrician, I have in mind some definite psychological skill in obtaining a small group of data which are of paramount importance in the prediction of postpartum psychopathological complications.

In order to describe these data I would prefer to present one or two, and preferably several, case histories which could serve us as a guide. Unfortunately, I find it impossible to follow my desire for the following reason.

Psychiatric histories are not of the same order as medicosurgical histories. In the greatest majority of medicosurgical histories, a change of name of the patient, or the omission of it, suffices to disguise the identity of the person under discussion. This would not be sufficient to disguise the identity of a psychiatric patient. In order to achieve such a disguise or concealment of identity in psychiatric cases, one would have to go into so many omissions and plain distortions that the clinical validity of the case would become at times rather doubtful. I shall therefore have to limit myself to a somewhat condensed and what might appear desultory recitation of certain clinical facts—even though in doing so I am aware that of necessity I run the risk of reducing the telling value of the clinical demonstration.

We must also remember in this connection that, when we speak today of psychological problems and of psychopathological reactions, we cannot avoid including the unconscious reactions and the unconscious conflicts. Whatever the orientation or the bias or the school of a given psychiatrist or near-psychiatrist

today, he does take into consideration the unconscious, even though he may feel moved on theoretical grounds to refuse to give it official, scientific recognition. This quasi-universal acceptance of the unconscious is, however, far from being a blessing, because the unconscious cannot be observed directly, is not tangible in any way. Its inferred existence is based on inferred evidence, and its enormous clinical importance makes it even more difficult to be very accurate. This I state rather in the spirit of regret that here we have one more example of the human limitation to our scientific omniscience. This said, I must dwell for a moment on an issue that has caused more confusion and conflict in psychiatry and psychoanalysis than any other issue of which I know.

The so-called tradition of common sense takes it for granted that motherhood is one of the most natural states and functions of womankind, and therefore one usually does not think of any special psychological impediment to motherhood. As a matter of fact, some mistakenly believe that motherhood is a cure for many difficulties; there are some who consider that even manifestly homosexual women may and ought to marry, and that these could have children with moral and psychological impunity as far as both the mothers and the children are concerned. The mistake in this trend is the unwitting conception of the whole process of pregnancy and childbirth as a physiological one only. The psychology (conscious and unconscious) of a manifest homosexual mother toward her physiological child is left out of consideration, yet it is of paramount importance. We talk of true maternal love on the part of a homosexual mother; yet the influence of the conscious *and* unconscious hostility toward the child is a factor of prime psychological and sociological, and therefore of medical and public health, importance. The child of such a mother cannot grow up into a normal, loving person. Such a child is destined for considerable trouble, with himself and with his environment.

I am leaving out here any discussion of the dangers such a wrong marriage and progeny almost always present to the marriage itself, and to the mental health of the father. That the mental health of the mother in question is endangered under the circumstances described seems beyond doubt.

Let us note the above-mentioned factor of the unconscious hostility of the mother toward her child, and let us say in passing that this unconscious hostility has its rather mysterious ways of conveying itself to the child and of provoking a considerable number of undesirable and at times directly pathological reactions.

Let us also note in this connection that the usual unconscious hostility of the father even to the as yet unborn child plays a considerable role in affecting the pregnant mother's psychological equilibrium. This hostility usually takes the form of apprehension, of anxiety. Human beings, even the most reasonable among us, are not very strong on knowing what is going on in their own psychological recesses. They are universally inclined to explain away their anxiety; in this process, a sort of emasculated common sense does yeoman's work and helps them not to understand very well what is going on. Thus an anxious expectant father may keep going on about his daily business, becoming

a little more irritable perhaps as the pregnancy progresses. But he usually hides the fact that his sleep may be affected, his dreams become disquieting, thoughts of adultery keep creeping in, and he becomes apprehensive lest the child come to this world deformed, stillborn, or otherwise injured, lest the mother fail to survive, lest the obstetrician fail at the last moment and cause something or other to go wrong with the mother or with the child.

This type of anxious, ruminative reaction is almost universal among expectant fathers; they are widespread at any rate. An observant and skillful obstetrician today may bring the expectant father within the orbit of prenatal care, and the obstetrician will be well rewarded for these efforts. For, while these universal reactions of expectant fathers *are* universal, and in this sense (and only in this sense) are "normal," proper handling of these fathers, proper warning that it is normal to be squeamish and apprehensive under the circumstances, proper assurances that what they feel is what any human expectant father might feel and that it is therefore best for them to talk it all over with the obstetrician and thus save the expectant mother unnecessary bewilderment, offense, anxiety, or discouragement; in a word, proper watching and management of the father may help discover in some such fathers the possible beginning of a severe neurosis or even psychosis (there *are* postpartum psychoses in men). An early psychiatric consultation might thus prevent an accentuation of the affective reactions of the pregnant woman, and mitigate and make easier to manage whatever psychopathological reaction the given woman might develop post partum.

Would that all this were so simple, complicated as it is; but there is another complication. The influence of Freudian theories on present-day psychiatry makes it necessary to try to make one more clarification. When Freud outlined his theory of sex, it soon became clear to him that his theory was based on the hypothesis that the psychosexual development of the human being fitted only the implied hypothesis that all human beings are created equal, that is to say, that in the beginning they were all men so to speak. This understanding led him to postulate the psychological principle that whereas man, if normal physically and mentally, grows from psychosexual infantility to psychosexual adulthood, and without any impediments into psychosexual parenthood, women, however, do not attain psychosexual motherhood directly; their psychosexual development must go through a complex and painful and sometimes dangerous (from the standpoint of mental health) masculine phase. We need not go into the details of this hypothesis. Nor do we need to contest it. This has been done before in the psychoanalytic literature, and sufficient doubt on this aspect of Freud's hypothesis has been cast by some orthodox Freudian psychoanalysts themselves.[2]

Suffice it to say that in this respect Freud's theory is peculiarly androcentric, that it contains some misogynous implications. And it is no error at all if we assume that motherhood is the singularly natural privilege of the woman, and that it is doubtful whether woman must go through a psychosexual phase of being a man before she attains her natural biopsychological

goal of motherhood. The theory of bisexuality, even in its sketchiest outline, would take care of many of the psychosexual problems with which the woman is confronted in living her role of a woman and in attaining her goal of mother.

For the purpose envisaged by this paper, it will suffice to say that a number of women who to all intents and purposes appear fully normal to the layman, general physician, and even psychiatrist labor unconsciously under the varying pressure of severe ambivalence toward motherhood—their own possible motherhood, I mean. I used the word *unconsciously,* and whatever follows here on this subject concerns pre-eminently the unconscious reactions of the woman.

Thus, a certain number of women have extremely severe hostility toward their own child within their womb. This hostility is at times overwhelming. The obstetrician will never see this hostility directly, but he is entitled to know some of the conscious derivatives or conscious results of such unconscious hostility. Such women frequently show almost no interest in children, any children (their own and those of others). In these days this fundamental lack of interest may be masked by our middle-class *mores* in accordance with which the mother frequently does not take care of her children; she just bears them and then leaves them in the hands of nurses and governesses. Yet it is really not difficult to detect the unmotherly mother and thus be on the lookout, as it were.

Such women more often than not prefer to have a girl than a boy, and there are cases of women who treat their sons as if they were girls. I know of a mother who used to call her boy "ma jeune fille," with corresponding consequences for the boy; the mother in this case had escaped serious psychopathological difficulties for many fortuitous reasons which did not save her from trouble, but kept the trouble fully masked to the uninitiated eye. Moreover, hers was psychologically a rather efficient way of living out the hostility she had felt toward the boy ever since he was born and throughout her life.

Any hostility in relation to any of the siblings, and especially in relation to the father, that the obstetrician might be able to elicit in the course of the pregnancy of this type of woman, by means of casual but deliberate anamnestic talk, might provide an invaluable clue as to what the future mother's unconscious attitude toward the forthcoming child may turn out to be. I cannot emphasize too forcibly how important it is to establish as early as possible during a pregnancy the presence and the severity of the unconscious hostility of the expectant mother toward her offspring. One of the methods frequently used nowadays in psychological diagnostic work is the method of obtaining information by means of various psychological tests. I am not a great admirer of any of these tests, because people are inclined to use them as the last word in psychological technique for uncovering the make-up of a given personality. A psychological test is at its very best an adjuvant to clinical evaluation, and not the evaluation itself.

For this reason I would consider it a wise procedure to use one test routinely, but leave the results to be evaluated by a clinical psychiatrist in

consultation with the obstetrician. If this procedure is followed, the obstetrician's psychological experience and acuity cannot help but increase and thus make his work more fruitful. The so-called clinical psychologist, the best one, cannot help but remain a psychologist; whereas clinical psychopathology, the work of medical men, can utilize to great advantage clinically, medicopsychologically, the work of the psychological technician, in the same way as the internist and surgeon and obstetrician utilize to great clinical and therapeutic advantage the reports which they obtain from the laboratory technician, be they in the field of microscopy or physiology.

I for one prefer the use of the Rorschach test. It is simpler, takes less time, puts the patient under considerably less strain than other tests. Moreover, the Rorschach test leads us in my opinion to greater insight into the affective structure of the person tested than other tests which seem to be constructed more on the purely intellectualistic level. The difficulty with the Rorschach test is that it must be given by a very competent person.

I have just implied that we are most interested in the affective structure of the patient. This is a point that may not be overlooked. The intellectual level is of little interest in the consideration of the problem under discussion, because a stupid mother may turn out to be a healthy and in this sense a normal mother. Nor are we interested in the purely rational (or rationalized) equipment of the woman, except in so far as it might reveal to us her unconscious attitude—and unconscious attitude means affective, emotional, or emotionally motivated attitude, which is always irrational and obscure.

It is this affective attitude, however, that holds the key to the psychopathology under discussion, and the central, most significant point in this attitude is the woman's reaction to the act of parturition. This attitude in the normal woman, while complex, is not difficult to observe and evaluate. The woman as a rule does not object to the pain involved in the act. The psychoanalyst is quite familiar with the role of physical pain in the act of parturition, and he knows that normally the suffering in question plays a beneficial psychological role in the whole act. So much so, that psychoanalysts for a long time suspected that the use of drugs and anesthetics during the very act of parturition to kill any vestige of pain has as a rule an unfavorable psychological effect on the mother and on her attitude toward the newborn child. I suspect that in so-called "natural childbirth" the woman is not actually relieved of the pain experienced during the act of parturition, but weaves this pain together with the ecstasy of the act of giving birth so that the pain itself does not stand out as an isolated reaction but becomes a part of the pleasurable experience. This is a psychological phenomenon known in psychiatry as a masochistic experience, which has been found by clinical psychoanalysts to be an integral, a psychobiologically necessary, part of healthy parturition.[3] With this observation we come to *the* most important element of the whole problem.

There are women who are psychologically so constituted that they are "unwilling," i.e., unconsciously unwilling, to yield the baby from their womb. They

"enjoy" being pregnant, they unconsciously (and some even consciously say it) want to be always, permanently pregnant; by permanently I mean not repetitively, but permanently. Since permanent pregnancy seems to be a gift that nature refuses to bestow on these women, they sometimes settle for repetitive pregnancies but with rather disappointing and at times disastrous results. I know of women whose desire for permanent pregnancy was combined with the horror of the natural termination of the pregnancy. As a result of this intense, agitated anxiety one such woman lost her baby before term; as if this were not enough, while claiming that she wanted no more children (she had living children already), she became repeatedly pregnant and repeatedly miscarried or was aborted "therapeutically" only to become "accidentally" pregnant again. I have known other women who went through very severe periods of agitation, crying, rebellious objections to everything and everybody for a long period post partum, and these women seem constantly preoccupied with the thought of becoming pregnant again. They yearn for the time when they will become pregnant again, and at the same time are preoccupied with obsessional, ruminative remembrances of how many things went wrong when they were last in labor: the obstetrician was wrong, the nurses were wrong, the husband was wrong, the hospital was wrong, the whole world was wrong—everything was and remains wrong as far as the management of her labor was concerned. This is a form of projecting a woman's own unconscious wish to stop labor and retain the fetus, into everything and everyone around her.

These women during their prepregnancy, or should I say interpregnancy, periods, usually present a great variety of obsessional, compulsive neurotic character traits, and they are usually very far from motherly people; they are poor housewives too, for that matter. They belong to what I might call the type of women who are anatomically and physiologically women but who seem to have rejected motherhood with varying degrees of intensity. It is this intensity of unconscious rejection of motherhood that one must learn to gauge clinically and to manage accordingly.

The best prevention of trouble in such cases is prenatal, psychiatrically guided management, and prompt postnatal psychiatric care. The avoidance of pregnancy does not help such women, since pregnancy is one of their most cherished goals. So-called therapeutic abortions are certainly of no avail; first, since these might precipitate a postabortive psychosis which is almost identical with the postpartum psychosis; and, second, since such abortions do not prevent the repetitive pregnancies which are but a constant reaccumulation instead of a solution of the difficulties under which sick women labor.

The problem, as you see and as I said at the beginning of this paper, is definite and clear only so far as the questions it raises. The answers to these questions are in the hands of the clinician whose job it is to accumulate more experience in the light of modern psychopathology.

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THE PROBLEM OF SPONTANEOUS ABORTION*†

I. A Combined Approach

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IN AN attempt to throw some light on the still largely unknown causation of spontaneous abortion, we began a few years ago a multidisciplinary approach to the problem. Our method is as follows:

1. Every patient with habitual or threatened abortion under the project is admitted to the hospital for three days. She is then seen by:

2. An obstetrician, who examines her thoroughly from the obstetrical-gynecological angle. She also has a complete physical examination and her past history is thoroughly explored.

3. A psychiatrist who interviews her, and a psychologist who subjects her to such tests as the Mental Health Analysis, the Rorschach, and selected cards from the Thematic Apperception tests. Some patients with habitual and threatened abortion who did not abort were seen by the psychiatrist throughout their entire pregnancy.

4. Certain biochemical and hormonal tests are carried out by a biochemist.

5. All abortuses are examined by a pathologist.

6. Once a week the entire group meets and discusses, *as a group,* each case coming under the project.

Our results fall into two large groups, negative findings and positive findings. On the negative side our findings have been of a type that do not support those theories of causation or cure that are based on certain deficiencies in diet, hormonal support, etc. On the positive side we have found certain changes in the placentas in cases in which abortion has occurred, and have gained the impression that the pregnancy hormonal levels in the blood vary considerably with emotional states.

We have studied in the manner described 135 cases, which are categorized in Table I. None of these cases were given any special treatment.

TABLE I. EXPERIMENTAL CASES

Total	135
Habitual	15
Aborted	67
(Of these 7 were habitual.)	
Carried on	68
(Of these 8 were habitual and 11 were premature.)	
Controls	24

*The work of the project has been supported by a Federal Health Grant throughout.

†Presented at a meeting of the Canadian Medical Association, Toronto, Ontario, June, 1955.

Approximately half of our patients aborted. Our survival rate was therefore very much the same as that reported by other authors[6] giving no special treatment (Table II).

TABLE II. SURVIVAL RATE IN THREATENED ABORTION

AGENT	AUTHOR	YEAR	NO. OF CASES	PER CENT CURED
No treatment	Crowder et al.	1951	37	57
No treatment	Guterman and Tulsky	1949	210	40
No treatment	Kotz et al.	1941	45	62
No treatment	Colvin et al.	1950	1,570	72

In detail our findings can be grouped as follows:

1. Exercise and Stress.—In an attempt to determine the validity of the widely held theory that certain forms of exercise and physical and emotional stress may be followed by abortion, we made careful inquires into the activities of our women in the period immediately prior to the onset of symptoms of threatened abortion. Table III shows the results in those who aborted and in those who carried on to term.

TABLE III. INITIATING FACTORS

INITIATING FACTOR	ABORTED (67 PATIENTS)	CARRIED ON (68 PATIENTS)
Intercourse	22	18
Car drive	12	14
Exertion	23	19
Emotional stress	15	23

While in practically all cases one or more of these factors were present, they were no more frequent in one group than the other. We believe, moreover, that these same factors are present in practically every pregnant woman. While it is possible that they act as a trigger mechanism in an unstable situation, we do not believe that they are the basic cause of any particular abortion.

2. Abnormal Diet.—It is practically impossible to conduct an effective investigation into diet since, even if a woman appears to be eating the proper foods in the proper quantities, there is no proof that these foods contain the proper food factors. There may be sufficient calories, but—depending on the soil in which it is grown—there is probably considerable variation in actual food values. After consultation with our dietitians we presented each woman under the project, and a small group of controls, with a questionnaire. As Table IV shows, about one-third of our project patients were eating abnormal diets as shown by low protein and food lacking in vitamin content, but so were the controls in approximately the same percentage. We were therefore unable to find any evidence that diet had played any real part in causing our project women to threaten to abort.

TABLE IV. DIETARY INVESTIGATION

	NO.	ABNORMAL DIET
Aborted	67	18
Carried on	68	19
Controls	24	5

3. Structural Uterine Defects.—By means of hysterograms done six weeks after an abortion we were able to demonstrate only two cases of possible uterine defect. In one case, with a history of a difficult breech extraction,

the internal os of the cervix was seen to be grossly incompetent. In another case there was a rather marked saddle effect at the fundus, suggesting a partially bicornuate uterus. Our findings, however, were in agreement with those of others, that there were twice as many retroverted uteri among those who aborted as among those who carried on.

4. Vitamin C Deficiency.—On the basis of a possible deficiency, several authorities recommend vitamin C therapy in threatened and habitual abortion, and claim a high percentage of success. We estimated the blood levels of this vitamin by the method of Roe and Keuther.[11] Table V shows our results.

TABLE V. VITAMIN C CONCENTRATION IN WHOLE BLOOD

WEEKS AFTER LAST MENSTRUAL PERIOD	MG. % BLOOD		STANDARD DEVIATION	
	NORMAL	THREATENING	NORMAL	THREATENING
0-16	0.68 (21)*	0.78 (69)	0.30	0.36
17-24	0.79 (32)	0.79 (18)	0.37	0.41

*Figures in parentheses show number of subjects in each group.

It will be seen that patients who threatened to abort up to the sixteenth week after the last menstrual period did not have lower vitamin C concentrations than subjects who carried through the same stage of normal pregnancy. In fact the mean value at the time of the threatening episode was a little higher than the mean concentration found in normal subjects. This difference, however, was not statistically significant ($0.2<P<0.3$) and from this we conclude that the vitamin C concentration was essentially the same in both groups. A similar comparison between normal subjects and patients who threatened to abort between the seventeenth and twenty-fourth weeks after the last menstrual period clearly shows that during this time the patients were not in a state of relative vitamin C deficiency when compared to the subjects who carried through a normal pregnancy ($P>0.9$). It is worth pointing out that all these four mean vitamin C concentrations are above the lower limit of normality, 0.5 mg. per cent.

The incidence of deficiency expressed as per cent (vitamin C concentrations lower than 0.5 mg. per cent) is approximately the same among the women who threatened to abort as among those who carried through normally to term (Table VI). When the patients who threatened to abort were grouped according to the outcome of the pregnancy, the incidence of deficiency was approximately the same among the women who aborted and those whose pregnancy proceeded following the threatening episode.

TABLE VI. INCIDENCE OF VITAMIN C DEFICIENCY EXPRESSED AS PER CENT

WEEKS AFTER LAST MENSTRUAL PERIOD	NORMAL PREGNANCY	THREATENED	ABORTED	CARRIED ON
0-16	29% (21)*	28% (69)	32% (34)	24% (33)
17-24	28% (32)	22% (18)	0% (5)	30% (13)

*Figures in parentheses show number of subjects in each group.

We were therefore unable, using the method of Roe and Keuther, to satisfy ourselves that vitamin C deficiency had played any important role in initiating abortion in our cases. As a result we are led to conclude that, if vitamin C therapy is in itself actually beneficial, it must be either because its effect is psychological, or because the type of patient who tends to abort requires a higher blood level of this vitamin than the woman who does not.

5. Vitamin E Deficiency.—We determined the vitamin E serum concentrations by the method of Quaife and associates[9, 10] and the results are shown in Table VII.

TABLE VII. VITAMIN E CONCENTRATION IN BLOOD SERUM

WEEKS AFTER LAST MENSTRUAL PERIOD	MG. % SERUM		STANDARD DEVIATION	
	NORMAL	THREATENING	NORMAL	THREATENING
0-16	1.48 (26)*	1.38 (67)	0.42	0.26
17-24	1.68 (38)	1.61 (18)	0.38	0.28

*Figures in parentheses show number of subjects in each group.

In women going through a normal pregnancy the concentration of vitamin E is higher in the later stage of pregnancy, which is in agreement with a number of reports in the literature. However, this increase is not quite statistically significant ($0.05>P>0.1$). The same pattern of increase was observed among the patients who threatened to abort and the difference between the two groups of patients is significant ($P<0.01$). When the patients and normal subjects at the same stage of pregnancy are compared there is no difference between them. At the 0 to 16 week period the value of P is between 0.2 and 0.3 and at the later period it is between 0.4 and 0.5.

The same conclusions are reached if expressed in terms of percentage of vitamin E deficiency. Using 1.06 as the lower limit of normality in the period 0 to 16 weeks, and 1.30 in the period 17 to 24 weeks, the results shown in Table VIII are found. It may be noted that the percentage of deficiency is the same in all groups.

TABLE VIII. INCIDENCE OF VITAMIN E DEFICIENCY EXPRESSED AS PER CENT

WEEKS AFTER LAST MENSTRUAL PERIOD	NORMAL PREGNANCY	THREATENED	ABORTED	CARRIED ON
0-16	19% (26)*	15% (67)	21% (33)	9% (34)
17-24	18% (38)	17% (18)	20% (5)	15% (13)

*Figures in parentheses show number of subjects in each group.

Scrimshaw, Greer, and Goodland[12] have reported subnormal vitamin E levels in patients who are threatening to abort, with a statistically significant difference between patients and controls in the 17 to 24 week period. It should be pointed out that both our patients and normal subjects exhibited higher vitamin E serum concentrations than those reported by Scrimshaw and associates for the same period of pregnancy. Since the number of subjects we have studied is adequately large for statistical analysis it appears unlikely that continuation of the study would disclose new information on this point. The higher values we have found in both our normal group and those threatening to abort suggest that perhaps the vitamin E intake of our population in general may be greater than that of the subjects studied by the American authors. This situation in turn could perhaps account for the normal rate of increase of serum vitamin E in women who threatened to abort. However, we could find no evidence in our cases of threatened abortion of a vitamin E deficiency.

6. Thyroid Deficiency.—In an attempt to determine this, we estimated serum cholesterol by the method of Bloor, Pelkan, and Allen,[1] with results as shown in Table IX.

TABLE IX. CHOLESTEROL CONCENTRATION IN BLOOD SERUM

WEEKS AFTER LAST MENSTRUAL PERIOD	MG. % SERUM		STANDARD DEVIATION	
	NORMAL	THREATENING	NORMAL	THREATENING
0-16	230 (26)*	214 (94)	56	38
17-24	249 (39)	254 (30)	47	41

*Figures in parentheses show number of subjects in each group.

Those of our patients who threatened to abort during early pregnancy appeared to have serum cholesterol levels lower than those who went through a normal pregnancy, indicating that they were in a relative state of hypothyroidism. The difference, however, is not significant ($0.2>P>0.1$). Similarly we have found no difference between patients and normal subjects 17 to 24 weeks after the last menstrual period ($0.7>P>0.6$). Serum cholesterol levels were higher in the later stage of pregnancy both in the case of the normal women and the patients, the increase being significant in the patients ($P<0.01$) but not so in the control group ($0.2>P>0.1$).

Our findings indicate that there does not seem to be real thyroid deficiency in threatened abortion. Perhaps the serum cholesterol level is too indirect and crude an index of thyroid function, and cannot detect small, yet physiologically important, changes in thyroid activity. Lum and Man[7] have shown that in women who abort the serum butanol-extractable iodines are sometimes lower than the expected range for normal pregnancy. The procedure used by these authors to evaluate thyroid function is more sensitive than the serum cholesterol estimation, and therefore it is possible that mild states of hypothyroidism may play a part in the causation of some abortions.

7. Sex Hormone Deficiency.—Sex hormones, particularly estrogens and progesterone, have been used widely in the treatment of threatened and habitual abortion, on the basis that these were deficient in the aborting woman. Except in the case of chorionic gonadotrophins we assayed these by biochemical methods. While our control data for estrogens, pregnanediol, and chorionic gonadotrophins agree with the normal levels published by Browne, Henry, and Venning,[2] the women on our project seemed to have a slightly lower average hormone level than the controls. Due, however, to the large variation, no statistical difference can be shown between those that aborted and those who carried on (Table X).

TABLE X. HORMONE ASSAY

GROUP	NUMBER OF PATIENTS	PER CENT CARRIED ON	PER CENT ABORTED
I. All hormones normal	44	68	32
II. All hormones low	21	29	71
III. Normal estrogen and progesterone; low chorionic gonadotrophin	14	63	37
IV. Low estrogen and progesterone; normal chorionic gonadotrophin	22	45	55
Total Study	101	46	54

In Group I where the estrogens, pregnanediol, and chorionic gonadotrophins were all within normal limits for the time of pregnancy, 30 patients, or 68 per cent, carried on, and only 14 patients, or 32 per cent, aborted.

In Group II where all hormones were low only 6 patients, or 29 per cent, carried on.

These figures seem to indicate that the prognosis is more favorable when all the hormone levels are normal and poorest when all are low, although some patients with entirely normal hormone levels aborted and some with all of them low carried on. On the whole, the evidence of deficiency, as determined by the methods we used, was unclear and not fully conclusive. This seems also the case where aborting women have been treated with these hormones. Our own results in cases outside this study have been very disappointing.

8. Emotional Factors.—During the past thirty years obstetricians have become increasingly aware of the importance of emotional factors as complications of pregnancy and this awareness has led to a closer cooperation with the psychiatrist in the solving of certain obstetrical problems.

Several papers and at least two entire chapters in as many textbooks in psychosomatic gynecology and obstetrics have been devoted to the emotional aspects of spontaneous and habitual abortion.[3, 13]

From the beginning of our project a great deal of thought has been given to the psychological and social factors affecting the adjustment processes of every woman from the beginning to the termination of her gestation. Assuming that the premature interruption of pregnancy is the outcome of the interrelationship of many factors, we felt that emotional and social stresses could be important links in the total chain of events leading up to an abortion.

Our method of psychiatric investigation was as follows:

1. Experimental Group—100 patients.
   - A. Clinical interview
   - B. Questionnaire which was devised specifically for this project and contained 70 items
   - C. Long-term observation of several patients
2. The data gained from A, B, and C were utilized to:
   - A. Classify 100 experimental patients into three groups
   - B. Items on the questionnaire were assessed and the trends studied
3. Control Groups:
   - A. Normal pregnancies undergoing same investigation as experimental group
   - B. Study of women in later stages of pregnancy at Prenatal Clinic

Space permits only a few general comments on our tentative conclusions concerning the psychiatric findings in women who threaten to abort. Certain personality changes seem to occur more frequently in those who do abort. On the other hand there seems to be no personality difference between those who, after threatening to abort actually do so, and those who, after so threatening, carry their pregnancy to, or almost to, term. Although there was considerable overlapping, our cases of threatened abortion fell into three main groups showing the following characteristics:

A. The Inadequate Reserve Group.—This group, which contained 44 of our 100 experimental cases, appeared to have inadequate psychological and physical reserves to cope with the demands of normal pregnancy. They were overly dependent, had difficulty in making their own decisions, were uncertain and anxious in their relations with others, were more or less confused about

their sex roles, and often ignorant of sex in general. They had anxieties and a tendency to depression that often dated back to childhood, although in general they expressed no particular fear of childbirth. The majority came from large families and had an unhappy childhood, due to such causes as a stern father to whom they could never come close, or a chronically ill and inadequate mother. On the whole they were a cooperative group, and welcomed the opportunity to discuss their difficulties. They were normally intelligent, and seemed to have greater psychological insight than the other groups. They could be summed up as women immature to most life situations, whose thinking centered mainly around their own needs.

B. The Independent, Frustrated Group.—This group, which consisted also of 44 women, was of a higher intellectual level and socially better adjusted. Their relations with their parents had been happier, and they were married as a rule to understanding husbands who were very often markedly neurotic. They were independent, had often been career women with special interests they had been reluctant to give up for marriage. They had mixed feelings about their feminine role, had often got pregnant for the husband's sake rather than their own, and were highly protective toward him—trying always to shield him from unpleasantnesses and inconveniences, and therefore unable to discuss pregnancy problems with him. While a few showed anxiety, most of them tended to obsessive and compulsive tendencies, with fear of failure. Physically they seemed quite healthy.

C. Mixed Group.—This group, which was small, consisted of a mixture of personalities. Some appeared well adjusted in most areas of life, others were unstable, shiftless, and neurotic.

A history of psychosomatic affections was rare in any of the three groups.

From the combined psychiatric and hormonal study of the small group of those who threatened to abort but did not do so who were followed throughout their entire pregnancy, we gained the impression that there was a correlation between emotional and hormonal factors. In these cases it was noted that emotional difficulties would appear to cause a lowering in the blood levels of the sex hormones, which would rise to normal again after a psychiatric interview or consultation. In any case, it was the impression of these women that such interviews and consultations helped them to make the best of pregnancy, and to adjust themselves better to its implications.

9. Pathological Changes in the Ovum.—The placentas and, whenever possible, the fetuses from 47 spontaneous abortions which occurred between the eighth and sixteenth weeks of pregnancy were examined. Placentas of 9 patients with threatened abortions who came to or near term were also studied. The controls consisted of 22 cases covering one to nine months' gestation, all with a normal obstetrical history. Some of these placentas were obtained from women who had therapeutic abortions for medical reasons.

There were 3 abnormal fetuses, one anencephalic, one cyclops, and one blighted ovum. The villi of the first 2 showed the unusual lesions just referred to, while the third showed the typical senile villi of a placenta at full term. The placental villi examined at term of those patients with threatened abortion who were ultimately delivered of living children, with 2 exceptions, showed no detectable variation from the normal. The exceptions ended in premature delivery, and scattered villi showed the same unusual alterations previously referred to.

Our investigations, therefore, do not support the findings of others[5] that there is a high percentage of fetal abnormalities in spontaneous abortion. We propose to investigate this more thoroughly in the near future, however.

The placental villi of 38 of the 47 abortions examined showed some unusual histological changes that do not appear to have been previously noted. The details of these changes have been described in No. II[4] of our series of papers on "The Problem of Spontaneous Abortion," already published. The following important points have been discussed in this paper.

In over half of our specimens changes were found in the villi which on staining proved to be plaques of degeneration, the result of tissue fibrinoid necrosis. This varied from a small plaque to a widespread affection of the villus. In others we found the whole villus had gone beyond this point to the stage of hyalinization.

The distribution of affected villi in a placenta is variable, there being loci of normal tissue adjacent to loci of abnormal, and comparatively few or many areas may be involved, varying from case to case. In any given placenta where the villi show this stigma, however, the stage of development between fibrinoid necrosis and hyalinization is fairly uniform, suggesting that when the damage originally occurred all the affected villi were injured at approximately the same time and the point at which they are seen in the evolution between necrosis and hyalinization depends on the duration of the pregnancy after the injury to the villi.

Since among other things collagen undergoes fibrinoid necrosis we wondered if collagen were the precursor of these changes we are finding in the villi. In support of this we did find varying amounts of collagen in at least 20 of the placentas.

The control specimens from 1 month to 9 months showed little or no collagen in the villi.

The question naturally arises, where does the collagen come from? Could it result from some chemical change in the ground substance of the villus? Such a change was demonstrated and found to be present in all of the cases showing either fibrinoid necrosis or collagen, and in 7 where no such lesions were found. It is thought that this change arises from an alteration of the villus ground substance. This substance appears to be normally a neutral mucopolysaccharide. By the use of a specific staining method we have found that this neutral mucopolysaccharide alters to an acid mucopolysaccharide in our abortion specimens.

It appears to us that the change in the ground substance produces a proliferation of fibrils to form collagen. This was previously suggested by Pearse[8] in his book on histochemistry in considering the general problem of the formation of collagen.

We may say that in some affected placentas three sets of changes can occur: (1) fibrinoid necrosis or hyalinization or collagen formation which appears in scattered villi; (2) a change (which appears in specific staining in the ground substance) which we take to be the alteration from neutral to acid polysaccharide, and which appears in all villi; (3) the surface epithelium of the villus degenerated. This last occurs late and becomes complete only on the complete hyalinization of the villus. No such lesions were found in the normal controls.

Could these lesions represent steps in a single process and be the last link in a chain of causation of spontaneous abortion? We ask ourselves what are the previous links. We are considering the ground substance. The question of allergens or other irritants causing such a change has been considered. Could it be that some slight derangement in the individual hormones of the pregnant woman plays a part? Could emotional changes cause these disturbances? We ask ourselves all these questions, but so far have come forward with no proof, but all will be investigated as the project is carried on.

Conclusions

In conclusion we can say that our investigation tends to show:

1. Our presently held etiological theories concerning habitual and spontaneous abortion should be regarded with the greatest skepticism.

2. That we confirm the usual findings of low hormone levels in threatened abortion.

3. That emotional factors seem to affect the hormone levels, and that psychological support and reassurance seem to enable some women threatening to abort to preserve their pregnancies.

4. That certain microscopic changes of a degenerative nature appear in the chorionic villi of the majority of women who abort.

5. We have been able to determine no definite causative factor for either the low hormone levels or the degenerative changes in the villi of aborting women. In short, we have no evidence to support any particular theory of the causation of abortion.

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THE PROBLEM OF SPONTANEOUS ABORTION

III. Psychosomatic and Interpersonal Aspects of Habitual Abortion*

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IN THIS paper we report studies of a habitual aborter, and attempt to demonstrate the importance of a long-term, detailed, interdisciplinary investigation to the understanding of a pathological process; the possibility of a relationship between emotional and hormonal changes; and the value of psychotherapy in the treatment of habitual abortion.

In pathological pregnancies, deviations from the normal homeostatic pattern in the maternal organism have been demonstrated. Browne,[5] Hain,[8] Jones and Delfs,[11] and others have reported low levels of estrogen, pregnanediol, and chorionic gonadotrophin in the urine of women who threaten to abort, or who have poor obstetrical histories. Abortion may also occur in the presence of apparently normal hormone levels.

It has been suggested that pre-existing emotional conflicts, or emotional disturbances occurring during the period of pregnancy may be contributing factors to spontaneous abortion.[4, 7, 14, 15, 17] Psychotherapy has been known to be successful in interrupting a series of spontaneous abortions. Emotional support appears to be one factor contributing to the successful treatment of habitual abortion, as mentioned by Berle and Javert,[2] Javert,[10] and Bevis.[3] The work of these authors seems to indicate that emotional factors may play an important role in spontaneous premature interruption of pregnancy.

Since no correlative studies between hormone levels and psychological changes during pregnancy are available in the literature, this aspect became a focus of interest in our long-term observations of our patients.

The psychiatrist sees these patients in weekly interviews of one hour. The patient collects urine for 48 hours prior to the interview. This collection is analyzed for chorionic gonadotrophin,[9, 12] pregnanediol,[16] estrogen,[1, 18] 17-ketosteroids,[6] and creatinine. A number of patients have been studied in this manner; the following seemed most interesting of these cases.

Case History

First Admission.—L. B. was first admitted Sept. 2, 1953, in the sixth week of pregnancy. No difficulty had been experienced during the present pregnancy; the patient came for investigation because previous pregnancies had ended in abortion. Between 1949 and 1953 this patient had had seven consecutive abortions before the third month of pregnancy, and therefore seemingly had a very small chance of carrying the present pregnancy to term.[13] Throughout all her previous pregnancies this patient was under competent observation and care.

*This report is part of the work of a multidisciplinary study, "Abortion Research Project" supported by a Federal Health Grant, under the directorship of Dr. W. R. C. Tupper.

After reviewing the history of her past pregnancies and on the basis of present findings the obstetrician stated that there were no gynecological or obstetrical reasons why these miscarriages should have occurred. The physical examination was negative.

The biochemical findings were as follows: cholesterol, 178 mg. per cent; vitamin E, 1.18 mg. per cent; vitamin C, 1.1 mg. per cent; all of which are within the normal limits. The hormone levels were found to be: estrogens, 0.11 mg. per 24 hours; pregnanediol, 2.5 mg. per 24 hours; chorionic gonadotrophins, greater than 163,000 M.U. per 24 hours; 17-ketosteroids, 5.0 mg. per 24 hours. The pregnanediol and estrogen values were low and the others normal for her period of pregnancy, as judged by our own data and the normal levels reported in the literature.*

The vaginal smear showed predominantly cornified cells with ragged edges, interpreted by the obstetrician as indicating a lowered estrogen level.

The psychiatric history condensed from a lengthy history follows. This was a 31-year-old, attractive, Protestant, married woman of average height and build. She was born in a small town where she lived until she went to college. She said that she had a happy childhood. She had no neurotic traits other than fingernail biting. She went to a large city where she continued her college education. She joined the Civil Service and remained in it until a year after her marriage at the age of 25 to a meteorologist. Since her marriage she has traveled about considerably due to frequent transfers of her husband.

Her father is a professional man of 58. He is described by the patient as a quiet, undemonstrative, and kind man, who wanted to see his children become independent as soon as possible. Here I quote from one of the interviews, "Even to catch a cold was a disgrace because it meant that we were not careful enough. This fight for independence made a woman of me." Her father always had a fear of tuberculosis and had several bouts of colitis.

Her mother was described as a home-loving, quiet person, who was very interested in her family. There was no marital friction between the parents, but the patient's mother maintained the peace by catering to her husband's hypochondriacal tendencies.

The patient had two sisters, aged 29 and 26. Both were married. The oldest did not become pregnant until the sixth year of marriage. During her only pregnancy, she had no difficulties, and gave birth to a normal child in uncomplicated labor. The second sister only recently married and has never been pregnant.

The patient was never seriously ill but she suffered from mild dysmenorrhea especially during her college years when she also had occasional bouts of diarrhea and her stomach would "go into knots." She had her menarche at age 12, having been adequately prepared by her mother. She reported no sexual difficulties in her marriage.

The husband was the same age as the patient. He was kind, thoughtful, well liked, and made friends easily. She knew him at least a year before marriage. During the period of study he was serving abroad.

She said about herself, "I have a temper and would like to fight at times but my husband doesn't. I was quite good at my job but I would rather keep house than work. I have a small circle of friends and I like parties and people around me."

On the basis of these investigations the patient appeared to be a physically and emotionally healthy woman.

On first contact with the psychiatrist, the patient was pleasant, cooperative, and showed a good understanding of the nature of the project. Although pessimistic about the outcome of her pregnancy, she was eager to participate in the study and willing to see the psychiatrist weekly and to collect the urine specimens.

The psychological tests suggested that she was a woman to whom appearances were very important. She tried to present a picture of herself as a normal, calm person living in a happy home. However, under the pressure of the tests this picture dissolved to show

*All biochemical and hormonal determinations are done in the Division of Biochemistry, Department of Public Health.

a tense, depressed woman living in a rather disturbed home and aware of her own precarious hold on security. Anxiety was aroused by many things in a world that she found rather unpleasant. However, she judged that her general social adjustment was satisfactory, that she had good friends, and was able to handle people well.

In spite of the patient's need to present a pleasant picture to "outsiders" she herself admitted that she was a person with inadequate emotional control, and one who was characteristically sensitive and tense. It can be said, therefore, that although this patient tried to impress others, she was reasonably honest in her dealings with herself.*

Arrangements for continued contact with the patient were discussed by the team, and approved by the patient, but before they could be acted upon, the patient had to be admitted to the hospital with signs and symptoms of threatening abortion.

Second Admission.—The patient was admitted to the hospital during the tenth week of pregnancy on Sept. 17, 1953, with pain and vaginal bleeding. Gynecological and physical examination showed no cause for the present signs and symptoms of abortion.

The hormone data were as follows: pregnanediol, 3.5 mg. per 24 hours; estrogen, 0.09 mg. per 24 hours; chorionic gonadotrophin, 48,000 M.U. per 24 hours; 17-ketosteroids, 8.0 mg. per 24 hours. Again the pregnanediol and estrogen values were below the normal range, the 17-ketosteroids were normal, and the chorionic gonadotrophins had fallen below the normal limit. This had occurred at the end of the waiting period between the first and second admissions.

It was interesting that the night before admission she dreamed of bleeding and aborting. The actual signs and symptoms appeared during the following day. The patient may have felt neglected during the interim of the first and second admissions.

She settled down, without other treatment than bed rest, and was discharged Sept. 19, 1953, free from bleeding and pain.

After this date the patient was followed on an outpatient basis. She was seen weekly for one hour by the psychiatrist and 48 hour collections of urine were analyzed each week for the previously mentioned hormones. The results of the hormone assays were not discussed with the psychiatrist until termination of pregnancy.

We will now present the highlights of the psychiatric follow-up, including the factors in the patient's life that seem related to hormonal changes.

Psychiatric Follow-Up.—

Oct. 9, 1953 (thirteenth week of pregnancy): This interview demonstrated the patient's emotional pattern. Periods of well-being alternated with periods of restlessness and depression. Inactivity and especially enforced passivity seem to have prolonged her depressive periods and induced at times withdrawal from human contacts. At this time the patient had a brownish vaginal discharge which worried her. The psychiatrist minimized the importance of this sign.

By the fourteenth week the excretion of estrogen reached the normal minimum, and remained at or near this level throughout the remainder of pregnancy.

Oct. 23, 1953 (fifteenth week of pregnancy): The patient was encouraged to follow her spontaneous tendency to activity. During this interview, she also stated, "You know, I have a theory. It must be mental. It might have been in my mind; I might have been too careful about my pregnancy. Now I carry on as though I wasn't pregnant." This statement seemed to indicate that the patient had begun to accept her relationship with the psychiatrist and to justify the interviews to herself. From this point the interviews were focused more on her total functioning, rather than on her pregnancy.

The chorionic gonadotrophins were falling, but this could be expected according to the normal curve of excretion.

Nov. 12, 1953 (eighteenth week of pregnancy): Although the patient accepted the new focus on her total activities, she began to resist the psychotherapeutic involvement. This attitude began to disturb the communication between the patient and the psychiatrist.

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*Thanks are due Mrs. Joan Morris for administering and interpreting the psychological tests.

By the eighteenth week the excretion of pregnanediol had increased to the normal minimum. The chorionic gonadotrophins were still falling.

Nov. 21, 1953 (nineteenth week of pregnancy): The interview of the nineteenth week revealed the consequences of communication difficulties between patient and psychiatrist. These difficulties gave rise to feelings of insecurity in the patient.

Nov. 28, 1953 (twentieth week of pregnancy): Upon realizing these communication difficulties the psychiatrist discussed them with the patient. Both the patient and the psychiatrist felt that this hour clarified the nature of their interpersonal relationship.

By this date the chorionic gonadotrophins had fallen to the lowest value since the beginning of this study—20,000 M.U. per 24 hours, at the very lower limit of normalcy.

Dec. 3, 1953 (twenty-first week of pregnancy): At this time the patient revealed that she had a diary covering a long period, and the next few interviews were spent in discussing the events and experiences surrounding the previous abortions.

Dec. 10, 1953 (twenty-second week of pregnancy): A certain repetitive pattern in behavior during the abortion period could be detected from her own descriptions in the diaries. On each occasion when the patient found herself pregnant, she feared that she might inconvenience her husband. Her need to remain independent was enhanced by pregnancy. When the process of abortion commenced, the patient denied it by trying to ignore it. Even when the symptoms were severe, she rejected help. The patient became restless, reaching a maximum of activity immediately after the completion of the abortion. During the period in which this material was discussed, she was depressed and overactive, mirroring her behavior and attitude at the time of her previous abortions. Following the interview of the twenty-sixth week, the psychiatrist finally realized the significance of this change in the patient's behavior. Therefore, between the interviews of the twenty-sixth and twenty-seventh weeks, the psychiatrist discussed this behavior pattern with her.

From an endocrinological point of view, this period from the twenty-second to the twenty-sixth week was characterized by a continuous, rapid fall in the chorionic gonadotrophins from 163,000 M.U. to 8,000 M.U., just below the normal limit, but probably not significantly so. The fall from the previous level was, however, dramatic.

Following the interview of December 10, the patient became more relaxed, until the Christmas holiday, during and following which she again became restless and upset. This was ascribed to mild external stresses.

Jan. 28, 1954 (twenty-ninth week of pregnancy): The psychiatrist again discussed her inner restlessness with the patient.

Feb. 2, 1954 (thirtieth week of pregnancy): The following week the psychiatrist was absent and the patient was without support during another stressful period.

The chorionic gonadotrophins fell to 2,000 M.U., the lowest value noted throughout the entire study, and definitely below normal.

Feb. 11, 1954 (thirty-first week of pregnancy): The patient was seven months pregnant and felt well. She was not as anxious and restless as during the two preceding interviews. She took her time and organized her affairs more efficiently. The chorionic gonadotrophins had risen to 40,000 M.U., a normal level.

Feb. 19 to Mar. 5, 1954: At this stage of pregnancy she was sufficiently reassured by her well-being so that she was able to make realistic arrangements for the arrival of the baby. This positive attitude to her pregnancy, and to the psychiatrist, prevailed until the patient gave birth to a normal full-term baby in natural childbirth and without complication.

Psychiatric Summary.—On the basis of the first interview during which the history was taken, and the observation of this patient over the period of thirty weeks, the following personality evaluation was derived.

The patient appeared very well adjusted on the surface. She maintained her calm exterior appearance at the cost of suppressed tension. During stress she either became lightly depressed or escaped into overactivity or both. Her history indicated that in adolescent and early adult life she suffered from dysmenorrhea and bouts of diarrhea,

which seemed to have disappeared since her marriage. She was sensitive to failure and to the reaction of others to her, and was loath to inconvenience others. Pregnancy seemed to represent a stress to her, to which she responded by becoming more independent, thus counteracting her biological and emotional needs.

Relevant to this psychiatric summary is the result of the following final psychological testing done just prior to the confinement:

"The picture was somewhat changed from that presented at the first testing. The patient was less tense and less productive on the Rorschach tests. Although she was not doing as much as she was capable of, what she did was more organized and logical. There was less variance of mood and less anxiety around her emotional responsiveness. The feeling of unpleasantness and tension formerly attached to her need for affection from others had lessened. She was now better able to accept this need. Although she was able to express her emotions more freely, there was still the necessity for gaining prestige and presenting a good front.

"Her relationship with her husband, judging from the psychological test material, seemed to have undergone some changes. Her feeling of responsibility toward him had increased, and there were more common interests, although it was still the husband who gave in to the wife when there was variance. She was able to admit that unpleasantness existed and she could verbalize a resentment toward her husband, and toward her mother. She saw children as a bother and inconvenience."

It appears that psychotherapy permitted the continuance of the pregnancy, possibly because it produced positive personality changes.

It will be noted that by the eighteenth week (November 12) with no treatment other than psychotherapy, the level of excretion of pregnanediol and the estrogens had climbed to normal values. In charting the results of the hormone assays, we were impressed by the fluctuations encountered from week to week in the level of the chorionic gonadotrophins, which are greater than would be expected on the basis of control assays, and the rises and falls do not coincide with those of a "normal" pregnancy.

It will be noted that at the ninth (September 17), twentieth (November 28), twenty-sixth (January 5), and thirtieth (February 2) weeks, the chorionic gonadotrophins reached low levels, falling markedly from the preceding levels. At these times the patient seemed to be under stress, some of which may have been induced by the tensions within the interpersonal relationship of the psychiatrist and the patient.

The pregnanediol excretion levels showed similar but not as marked fluctuations. The estrogens showed a steady slow increment, but remained at or slightly below the normal minimum throughout pregnancy.

Since the study of this patient several others have been followed in equal detail, and confirm some of the observations in this case.

Comment

Although we are well aware that any general conclusions drawn from the study of only one patient may be misleading or even invalid, we feel that the presented case is of sufficient interest to warrant a report. The patient discussed in detail serves as an internal control, since her history of seven consecutive abortions indicates that unassisted she seemed to have a very small chance of carrying a pregnancy to a successful conclusion. Therefore it seems reasonable to assume that psychotherapeutic contact may have contributed to the successful conclusion of her pregnancy.

Any treatment, if it is a prolonged one, is of necessity associated with attention and support from the physician which may gratify a specific need of the patient. This is a factor common to many of the courses of therapy prescribed in threatened abortion, and may well be a factor in the measure of success which they achieve. The specific therapy offered the patient discussed

in this paper may be analogous to the more general aid offered by the physician in connection with other treatment. We have the impression from the larger group studied that the attention the women receive while undergoing study is of benefit to them. The majority of these women seem to be of an immature, dependent type, either receiving inadequate support from their husbands and social group, or unable to utilize the available support even though needing it.

This study also seems to indicate the importance and potency of interpersonal contacts between investigator and subject, in research studies as well as during treatment of all kinds. The investigator may find it difficult, if not impossible, to avoid interpersonal involvement, thus altering the processes under investigation and consequently the results obtained. In our own study, we see indications that stresses of all kinds but especially of communication difficulties between patient and psychiatrist coincided with an alteration of the level of the chorionic gonadotrophins.

Summary

1. A long-term study of a successful pregnancy in a patient with a history of seven consecutive abortions and no living children is discussed. Obstetrical, biochemical, hormonal, psychiatric, and psychological data are given, and a possible correlation between psychological and hormonal findings pointed out.

2. The role of psychotherapy in the treatment of spontaneous abortion is emphasized.

3. The research implications of the interpersonal relationship between investigator and patient are considered.

For the steroids used in setting up the analytical methods we are indebted to the following:

Dr. E. Lozinski and Dr. A. D. Odell of Charles E. Frosst and Co. for the estradiol and estrone; Dr. G. A. Grant of Ayerst, McKenna & Harrison for the pregnanediol; Dr. F. E. Willson of Parke, Davis & Company for the Theelol.

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A NEW EXTERNAL TOCOGRAPH

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THE mechanism of uterine contraction during labor has engaged the attention of obstetricians for many years. Therefore investigators have attempted to estimate the expulsive forces of the contraction, and also to record graphically the uterine activities.

There remain many problems, however, in relation to the physiology of uterine contractions and the pathology of abnormal labor, yet to be studied. While it is true that the measurement of uterine contractions alone does not provide a solution for all of these problems, such measurement does provide an effective way to understand the physiology and the functional pathology of labor and expulsive forces.

The earliest attempts at obtaining a graphic record of uterine contractions were made by Schatz[1] in 1872, using the internal-balloon method. Since that time numerous investigators have devised a variety of instruments for recording the forces of uterine contractions in pregnancy and labor. Such graphic recordings of uterine activities have been classified as internal, external, and electrohysterographs.

The disadvantage of internal tocography, however, is that it allows the possibility of introducing infection into the uterus, and the risk of rupturing the membranes. In order to place the receptor, analgesia or anesthesia may be necessary, and these are obviously not suitable for all stages of labor.

In contrast, the external method leaves no possibility of infection or of rupturing the membranes. Nor are analgesia or anesthesia ever required. However, several disadvantages and limitations of external tocography have been recognized in the past.

In 1947 Reynolds[3] made a significant improvement over all former mechanical methods. He advocated the removal of the body-circling belt used in former measuring devices, through which uterine activities could not be recorded sufficiently accurately. In place of the belt he introduced a multichannel tokodynamometer (called TKD) which employs a strain gauge to act as a mechanoelectrical measuring device.

This instrument is both sensitive and accurate, and permits the study of the origin, spread, and dissipation of the waves of contraction over the surface of the uterus. It also provides a way to understand clearly the effects of analgesics, anesthetics, oxytocics, and other drugs on labor. Furthermore, Reynolds[2, 4] has derived an excellent conclusion: i.e., the concept of coordinate uterine contraction with "fundal dominance" and "gradient of diminishing activity."

However, because of the limited circle of the finger due to its relative immobility (0.0015 inch) the TKD is unable to record the second stage of labor satisfactorily. To quote Reynolds, "When the external method of recording uterine contractions is used it usually is not feasible to record contractions throughout the second stage of labor. It has been done in a few instances, without dramatic results. . . ."[7]

Through the new external tocograph I believe that I have been able to overcome that defect. The new external tocograph here described has made possible the recording of both normal and abnormal labor in all stages.

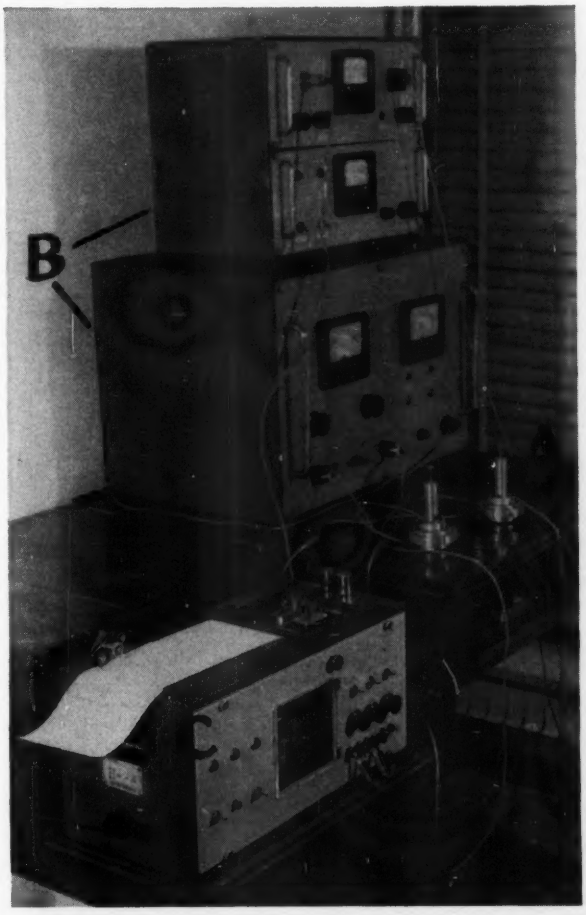

Fig. 1.—The two-channel external tocograph assembled. *A*, Receptors. *B*, Amplifier. *C*, Recorder.

Construction

The tocograph has three main components: the receptors, the amplifier, and the recorder (Figs. 1 and 2).

1. *The Receptors.*—Each receptor is composed of a brass ring with an internal diameter of 4.8 cm., through the center of which protrudes a metal finger (Figs. 3 and 4).

Contraction of the uterus results in an increase in its curvature, thus bulging of the uterus. This bulge causes unequal pressure against the ring and the finger. The finger thus acts as a transmitter of the contraction pressure between the abdomen and the transducer.

The transducer utilizes the variance of inductance. In other words, two coils are connected (parallel) to each other and compose two parts of a bridge. The transducer is constructed in the so-called "push-pull" form. Thus, as the inductance of one coil increases, that of the other decreases contrarily.

The metal finger moves in an upward and downward direction, as shown in Fig. 4. As the finger moves it produces unbalanced electric current flows. This unbalanced flow of electric current thus generated is closely correlated with the movement of the metal finger. The micrometer attached to the recorder indicates this unbalanced current flow, and the pen-motor attached to the recorder thus records the uterine activity in curves.

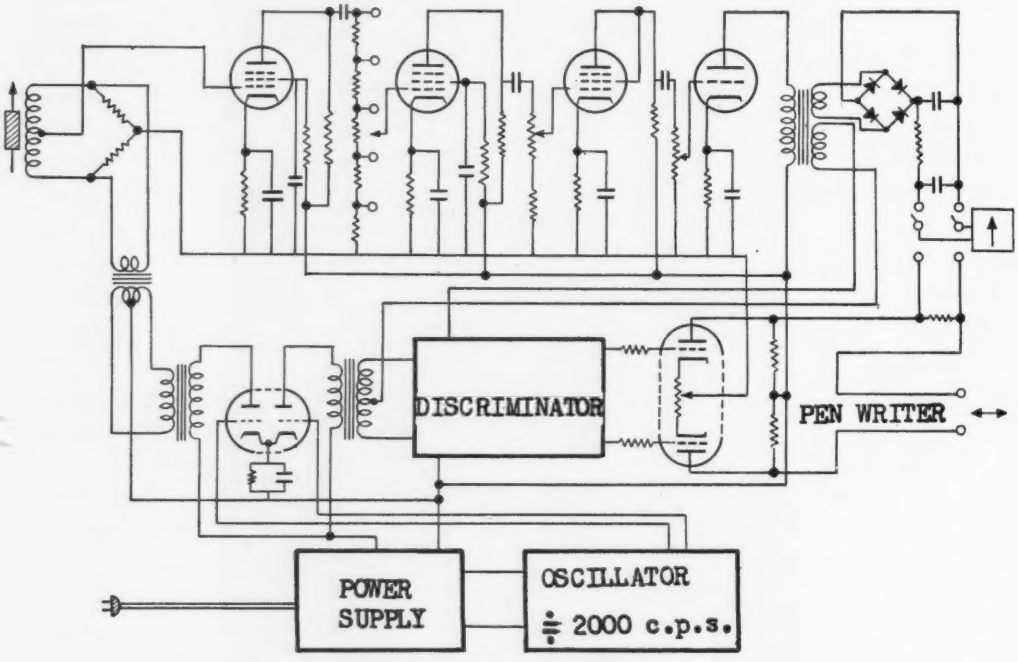

Fig. 2.—A single-circuit of the external tocograph.

One of the original characteristics of this new transducer is that the capacity of the finger to move is increased. The transducer is constructed in such a way that we can keep perfect electrical lineality with a maximum range of 8 mm. Therefore, I can record uterine activities at every stage of labor and under any difficult conditions without error.

Notice that the tip of the metal finger (i.e., the part which presses against the abdominal wall) is semispherical. Also, the handle at the top of the metal finger is attached at a right angle to the axis (Figs. 3 and 4). Because of this construction the tocograph is not influenced by normal respiratory and fetal movements.

To explain further, as a result of experiments I have discovered that if the tip of the metal finger is too small the tocograph will be easily influenced both by normal respiratory and fetal movements, and also by abdominal pressure.

This is true regardless of how taut or loose the vertical movement of the finger may be because the defect lies in the plunger itself; i.e., if the tip is too small it will press too deeply into the abdominal walls and the subcutaneous adipose tissue.

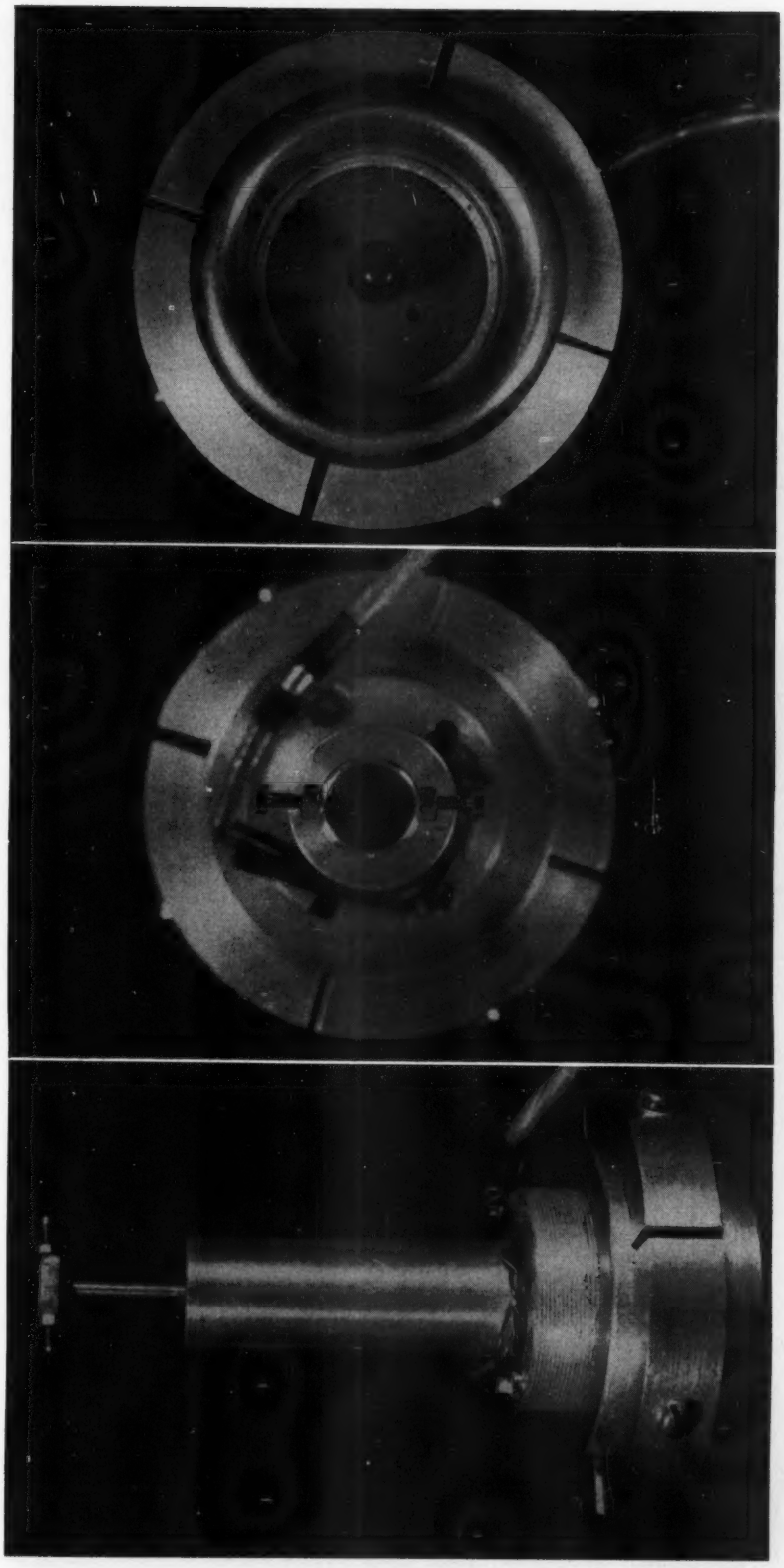

Fig. 3.—The receptor.

On the contrary, if the metal finger is semispherical and larger than that of the original TKD, it is less influenced by respiratory and fetal movements, and is thus able to record uterine activities accurately.

These are the main points in which I differ from the original design by Reynolds and his associates.[3]

2. *The Amplifier.*—The amplifier of this transducer is of the amplitude-modulate amplifier type. The alternating current (frequency 2,000 c.p.s.) generated by an oscillator is transmitted into the two coils of the transducer which compose the bridge.

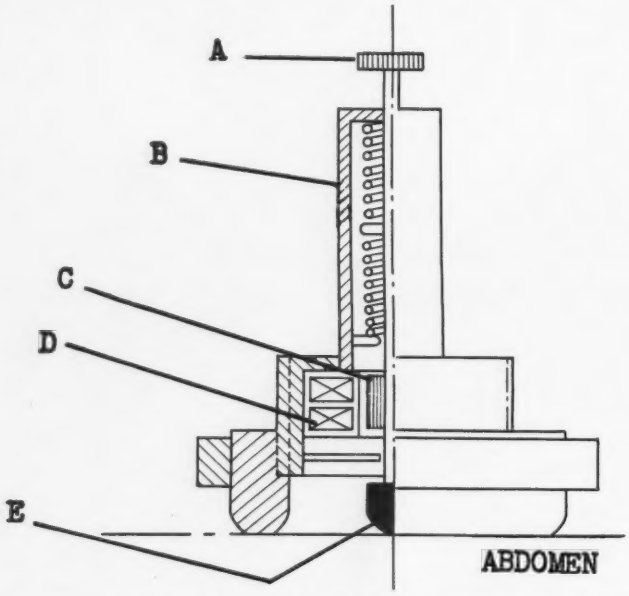

Fig. 4.—Construction of receptor. *A*, Spindle. *B*, Spring member. *C*, Core. *D*, Coils. *E*, Contact point (finger).

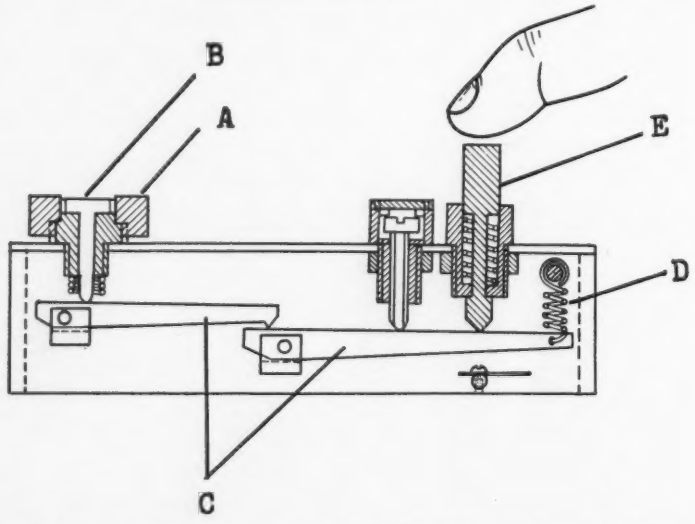

Fig. 5.—Calibrator. *A*, Control unit panel. *B*, Finger base. *C*, Lever system. *D*, Spring member. *E*, Button.

Turn the on-off switch to the on position. After several minutes, place the receptor on the control unit panel (*A*), push the button *E*, to give the finger amplitude.

Take care in calibrating the sensitivity of the amplifier in order to keep the amplitude of the pen-motor constant.

The unbalanced current flow generated by the movement of the iron core at the center of the metal finger is transmitted through another cable into the amplifier and, after amplification and output detection, it is then transmitted (as direct current) into the meter and the recorder.

However, in case the iron core should move down from the center of the coils (i.e., should the patient's abdomen contract unexpectedly), unbalanced current flow is also generated. This current flow is then amplified and mistakenly recorded on the plus side. In order to eliminate this error I have attached a discriminating circuit to the amplifier which is equal to the circuit of the ordinary strain-gauge meter.

Since the amplifier must operate for long hours, to insure a constant flow of current I have attached a vacuum tube voltage regulator and a stabilizing transformer. The distance between the transducer and this amplifier may be 10 to 15 M. (30 to 50 feet).

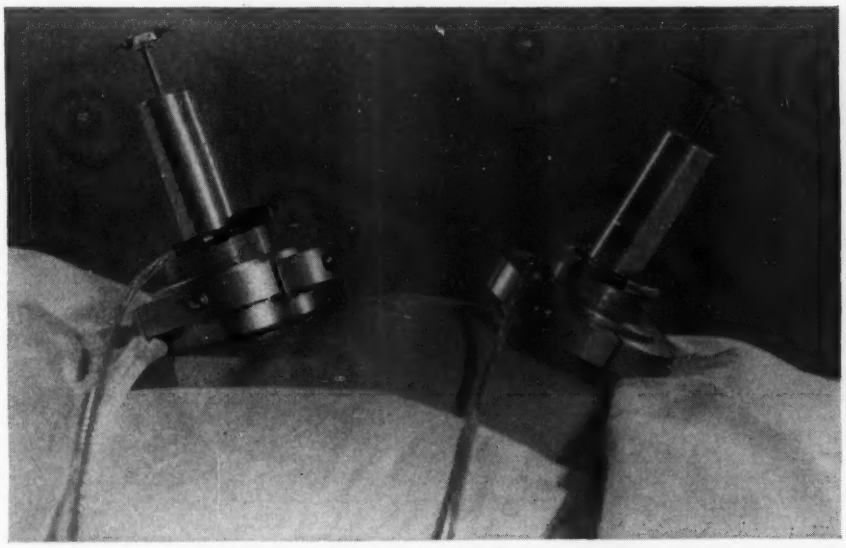

Fig. 6.—The receptors in place on the abdomen. The receptors are affixed to the abdomen by a double-coated plaster applied to the base of the rings.

3. *The Recording Unit.*—The recorder employs an oscillograph with a two-channel direct ink writer.*

The sensitivity of the pen-motor is as follows:

Coil resistance	10 kilometer ohms
Natural frequency	3 c.p.s.
Pen length	130 mm.
Deflection	100 mm.
Sensitivity	10 mm./Ma.

The recorder is fitted with a 50 M. (160 foot) roll of cross-section paper, which is capable of recording at a speed of 28 mm. per second, and will record for 30 hours successively.

Directions for Use

Having connected the receptors, the amplifier, and the recorder, turn the on-off switch to the on position. After waiting several minutes, set the receptor on the control unit panel of the calibrator (Fig. 5), giving the plunger a certain amplitude. One must use extreme care when adjusting the sensitivity of the amplifier in order to keep the amplitude of the

*Nihon Koden Kogyo Kaisha—Tokyo, Model WI-4.

pen-motor constant. When more than two channels of use are required, it is necessary to keep the sensitivity of each channel equal. If one is careless in regulation, the recorded contraction curves will be inaccurate.

When the above preparations are completed, paste a double-coated plaster on the base of the brass ring of the receptors, and affix the receptors to the anterior abdominal wall.

The patient is kept in a supine position during the process of measuring. She may eat and drink during the time of measurement, since this will not affect the recording.

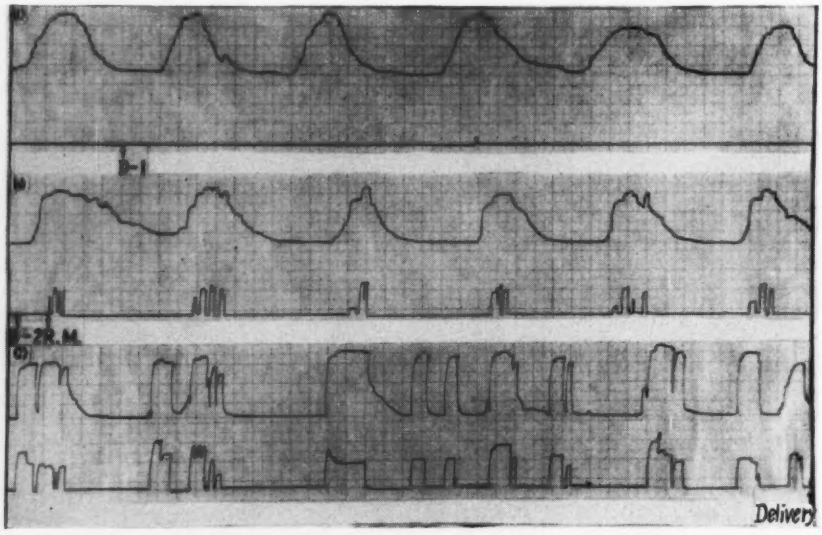

Fig. 7.—A section of the record of uterine activity in normal labor (para 0) in fundus (top) and the lower parts of the uterus (bottom).
a, First stage of labor. *b*, *c*, Second stage of labor. *D-1*, Cervix 3 cm. *D-2*, Cervix 10 cm. *R.M.*, Rupture of membranes.

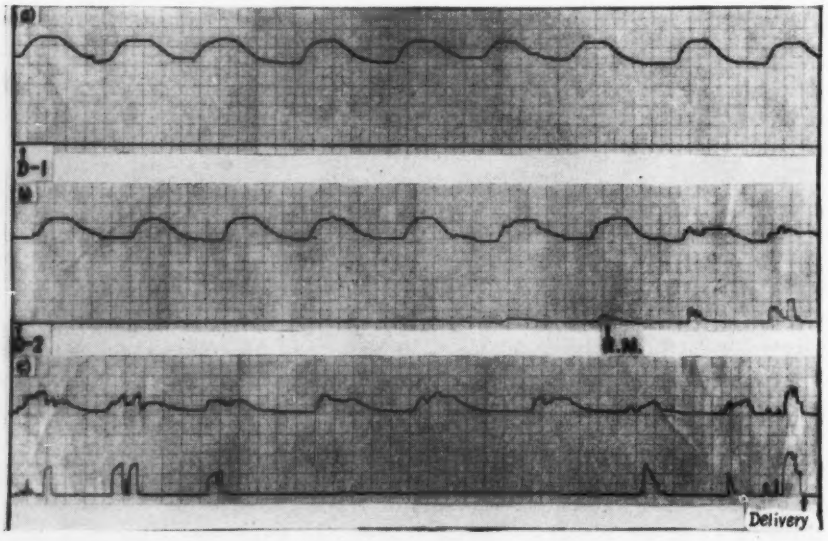

Fig. 8.—A section of the record of uterine activity in normal labor (para ii) in fundus (top) and the lower parts of the uterus.
a, First stage of labor. *b*, *c*, Second stage of labor. *D-1*, Cervix 4 cm. *D-2*, Cervix 8 cm.

Treatments (injections, enemas, catheterization, etc.) can be carried out during recording. Rectal and vaginal examinations, the general status of the patient, and the status of the fetus (position, descent, and heart rate) can all be ascertained.

Advantages and Limitations

1. This instrument enables us to make a comparative study of the recorded uterine tonus. It cannot determine the real tonus, however, since it is difficult to determine the absolute figure of the intrauterine pressure by using the external method.

2. The advantage of this new device is that it is constructed in such a way that, while recording labor pains, the vibrations caused by taking food and drink are not recorded. Thus it is possible for the patient to eat and drink during the time of measurement.

We cannot, however, prevent disturbances in the graphic curve caused by vomiting or coughing.

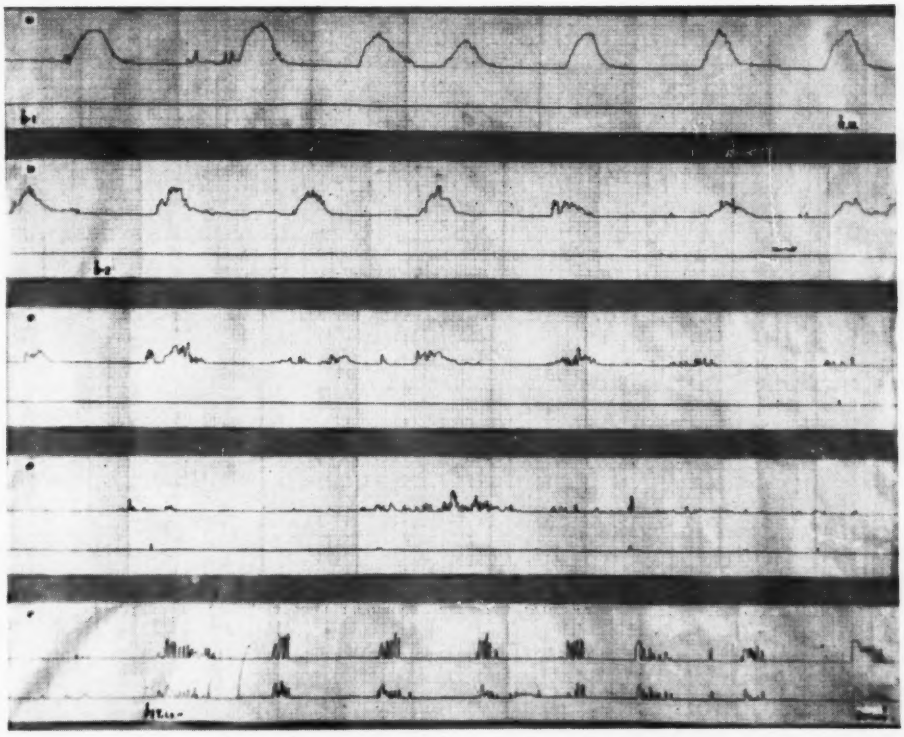

Fig. 9.—Secondary uterine inertia (para 0).

a, First stage of labor. *b*, *c*, *d*, *e*, Second stage of labor. *D-1*, Cervix, 8 cm. *D-2*, Cervix, full dilatation. *R.M.*, Rupture of membranes. PIT.i.v.; intravenous Pitocin drip infusion (10 units of Pitocin, 1,000 c.c. of 5 per cent dextrose in water).

3. In treating a woman of normal physical constitution with this instrument we can make a full measurement, regardless of abdominal fatness or thinness, by freely selecting the best location upon the abdominal wall. In the case of a woman with an abnormally fat abdomen, however, there will be times when it will be impossible to make an adequate measurement of the lower uterine segment.

Fig. 10.—Elderly primipara, 35 years old, low forceps.
a, First stage of labor. *b*, *c*, Second stage of labor. *D-1*, Cervix 6 cm. *D-2*, Cervix 7 cm. *D-3*, Cervix 10 cm. *R.M.*, Rupture of membranes. PIT.i.m., Pitocin, 0.2 c.c. intramuscular injection.

The two-channel recordings of this instrument are shown in Figs. 7 to 10. Many other recordings in labor, normal and abnormal, will be described in detail and illustrated in other papers.

Summary

1. The new external tocograph enables us to record uterine contractions during labor, by recording the variance of the abdominal wall (coinciding with the uterine activities), using a fixed receptor on the wall of the abdomen, and utilizing the amplified variance of inductance.

2. This instrument is a very accurate recorder of the uterine expulsive forces of the contraction. In order to exclude impure artifacts, the body-encircling belt is removed. Therefore this instrument overcomes the most serious defects of previous recording devices.

3. By the use of this instrument I can measure the uterine contractions during every stage of labor. Also, I can minimize the influence of vibrations due to natural breathing and body movements. Furthermore, this may be used to measure uterine contractions in abnormal labor.

In the construction of this instrument I am deeply indebted to Dr. Michitaka Kaku, professor of the Department of Obstetrics and Gynecology, Kumamoto University School of Medicine, without whose encouragement, guidance, and technical advice I could not have succeeded.

I also wish to thank Mr. Shiro Takashima of Nihon Koden Kogyo Kaisha for his valuable technical assistance.

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INTRAVENOUS IRON AS AN ALTERNATIVE TO BLOOD TRANSFUSION IN LATE PREGNANCY

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CONSIDERABLE interest has developed in the last few years in the use of parenteral iron in pregnancy. The increased requirement of iron in pregnancy is such that, while oral therapy is almost always efficacious, at least 60 to 90 days of such therapy is required to correct an established deficiency.[1, 2, 9]

Several investigators have demonstrated excellent response to various forms of parenteral iron therapy, anemias of rather marked degree having been corrected in a fairly short time.[3-5, 10-12] In our clinic, we participate in the care of a group of medically indigent women who characteristically have poor dietary standards and considerable parity. For this reason, we have found marked third-trimester deficiency anemia a serious and all too frequent problem. It has been our practice to transfuse patients in the last trimester who have hemoglobin levels below 8.5 Gm. We have long been dissatisfied with the fact that we have had no alternative to blood transfusion in treating marked anemia of the late third trimester. The dangers of blood transfusion are alarming and it has been shown that they carry a mortality rate greater than that associated with appendicitis, or with ether anesthesia.[6, 7, 8, 13]

This study was undertaken in order to determine to what degree intravenous iron might be a satisfactory substitute for whole-blood transfusion. The women studied were clinic patients in the Herman Kiefer Hospital prenatal clinic. All patients were Negro except one, and all had been referred to the Anemia Clinic for special management because of having hemoglobin levels below 9.5 Gm. All subjects except 4 were in the last trimester; these 4 were in the middle third of pregnancy and had hemoglobin levels under 8 Gm. Although no attempt was made to exclude them, it turned out that the series did not include any women with the sickle trait or sickle-cell disease. The patients were studied by means of hemoglobin, red blood cell, and hematocrit determinations made immediately prior to therapy, and at one-week, and again at two-week intervals following the beginning of therapy. In addition, routine sickle-cell preparations were also studied prior to therapy.

Technique of Administration.—Saccharated iron oxide* was given intravenously in doses of 100 mg. (5 c.c.) daily for 5 consecutive days. We employed a No. 21 needle on a 10 c.c. syringe containing the 5 c.c. single dose. Following venipuncture we allowed 5 c.c. of blood to fill the syringe before injecting the entire 10 c.c. This diluted the preparation in a manner consistent with the manufacturers' recommendations, and thereby facilitated

*The saccharated iron used in this study was Feojectin, supplied by Smith, Kline & French Laboratories.

slow administration and the earlier detection of perivenous extravasation. With the use of this technique, each patient in this study received 500 mg. of saccharated iron intravenously.

Results.—Twenty-six patients were studied for one week after the day therapy was initiated.

Average initial hemoglobin	7.9 Gm.	Average initial hematocrit	26.9 per cent
Highest initial hemoglobin	9.4 Gm.*	Highest initial hematocrit	33.0 per cent*
Lowest initial hemoglobin	5.2 Gm.	Lowest initial hematocrit	24.0 per cent

After one week of therapy, the average hemoglobin response was an increase of 1.0 Gm., and the average hematocrit response was an increase of 1.5 per cent.

Of these 26 patients, 20 were followed for an additional week. The average total hemoglobin rise for the two-week period was 1.82 Gm., while the average total hematocrit rise for the two-week period was 3.7 per cent.

One patient with an initial hemoglobin level of 8.8 Gm. failed to respond at all during a three-week period of intravenous iron therapy. Anemias other than those of the iron-deficiency type were ruled out by blood smears, corpuscular indices, fragility tests, and finally by bone-marrow examination. During the period immediately following therapy, this patient required hospitalization for severe pyelonephritis. At the end of the third week following the initiation of therapy, bone marrow examinations showed only a shift in the myelocyte series consistent with a response to acute infection. Since the patient was at term, it was considered necessary to treat her with blood transfusion. This is an example of failure of intravenous iron therapy in a patient whose anemia was complicated by severe kidney infection.

Side Effects.—A total of 130 injections were given to the 26 patients. A mild chill followed one injection; flushing and mild nausea followed 3 others. Perivascular extravasation occurred 6 times, resulting in discomfort for a few hours only. At no time was it necessary to discontinue or postpone therapy.

Summary

Over a four-month period, the 26 patients in this series were considered as candidates for blood transfusion because they had hemoglobin levels below 9.5 Gm. in late pregnancy. In all but one of these patients, the anemia was adequately corrected by the administration of parenteral iron. The average patient was cured of her anemia in from one to three weeks, regaining her hemoglobin at the average rate of 1 Gm. per week.

The reactions observed were not of significant importance, and never made it necessary to omit medication. The average rise in hemoglobin after one week of therapy was 1 Gm. Within two weeks of the initiation of therapy, the average hemoglobin increase was 1.8 Gm.

It is our conclusion that parenteral iron therapy is valuable not only in the effective and rapid treatment of severe iron-deficiency anemias of pregnancy, but that it is a very satisfactory alternative to blood transfusion, even late in the third trimester. Furthermore, intravenous iron therapy is probably safer than blood transfusion for the patient.

*The average initial hemoglobin on our service is 10.8 grams; the average hematocrit is 32 mm.

I wish to acknowledge the help and encouragement given by Drs. Charles S. Stevenson and Harold L. Fachnie, respectively Chief and Assistant Chief Obstetrician of Herman Kiefer Hospital, and to express appreciation for permission to do this work to Drs. Dale Barrett and Harold Longyear, respectively Director of the Division of Maternal and Child Welfare, and Prenatal Clinic Obstetrician, Detroit Department of Health. To Dr. Lorraine Sievers, who is in charge of the Anemia Clinic, goes my gratitude for her help and interest.

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Gynecology

THE SIGNIFICANCE OF POSITIVE VAGINAL SMEARS IN EXTRAUTERINE CARCINOMAS*

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THERE are few reports regarding the cytological diagnosis of extrauterine cancers by vaginal smears and this suggests that the occurrence of cancer cells in such smears in cases of extrauterine malignancies is relatively rare.

Frech[1] in 1949 reported one case of primary adenocarcinoma of the ovary which was diagnosed by vaginal smear. Simultaneously, Kraushaar, Bradbury, and Brown[2] have studied the exfoliative cytology in a series composed of 5,314 consecutive adult female admissions, representing three different segments of the population. They found malignant cells in smears from a case of adenocarcinoma of the rectum which involved the vaginal wall, and two cases of ovarian carcinoma without involving the uterus. No detailed cytological descriptions were given in their article.

Wachtel and Plester[3] were able to detect one case of ovarian carcinoma in a survey comprising 2,550 vaginal smears collected from the posterior fornix. The cells in the smears were not seen in clusters typical of uterine carcinoma, but appeared singly and were few in number. McGarvey[4] presented one case of serous cystadenocarcinoma of the ovary, with malignant cells in the vaginal smears, of a 37-year-old woman with a palpable ovarian tumor. He stated that the exfoliated malignant cells of the ovary cannot be detected in the vaginal smears until the tumor has broken through the capsule of the ovary, and such a tumor will be sufficiently large to be readily palpated. However, Umiker and Skeen[5] described malignant cells in the vaginal smears of a patient with an ovarian carcinoma, prior to the development of symptoms or signs referable to that tumor. Repeated pelvic examinations disclosed no enlargement of the ovaries and the patient had no gynecological complaints.

The Vincent Memorial Hospital[6] has reported one case of malignant teratoma of the ovary from which a group of cells were found to be characteristic of malignancy. In addition to these, cells from malignant tumors of the ovaries, as detected by the vaginal cytology method, have been illustrated by Masset and Nuovo,[7] Foot,[8] and Papanicolaou and Traut.[9]

*Presented at the Third Annual Meeting of the Inter-Society Cytology Council, Cleveland, Ohio, Nov. 11, 1955.

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Fig. 1.

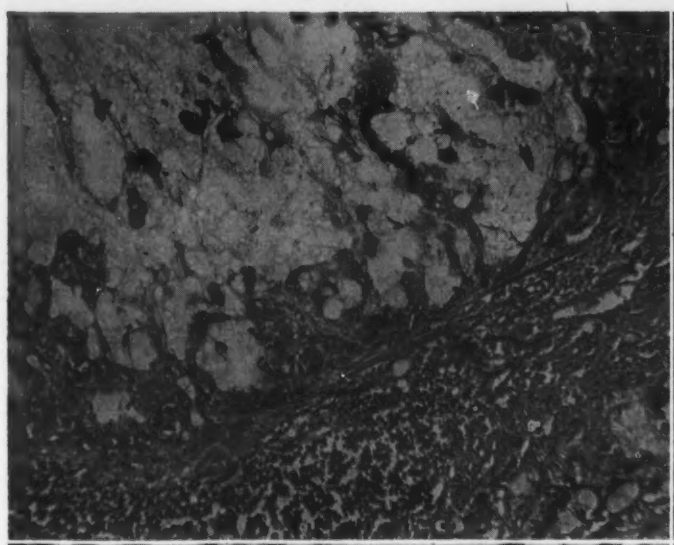

Fig. 2.

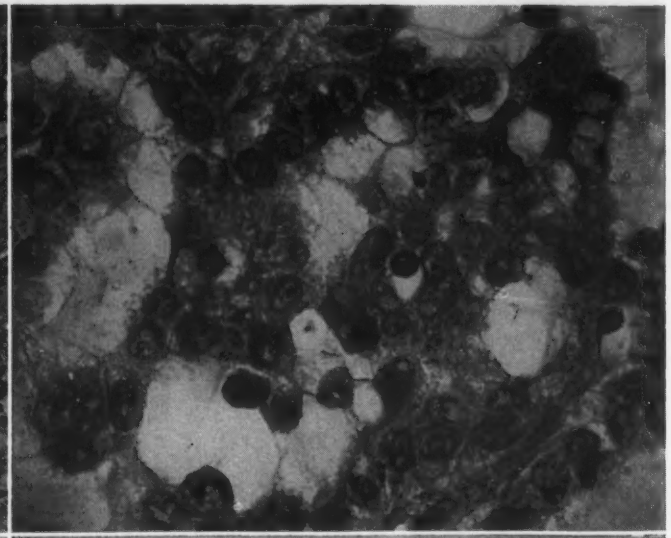

Fig. 3.

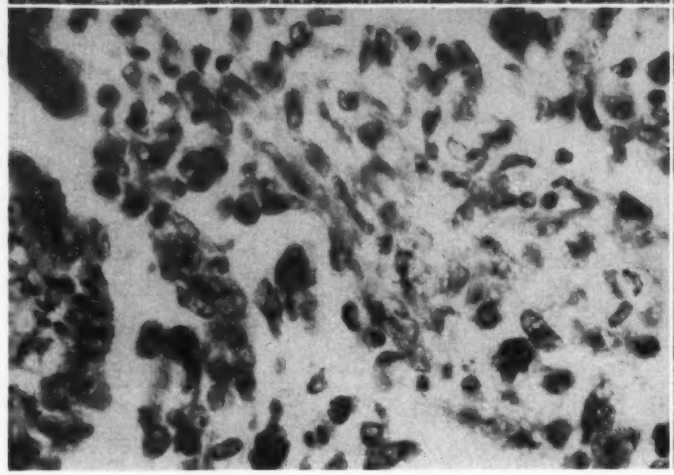

Fig. 4.

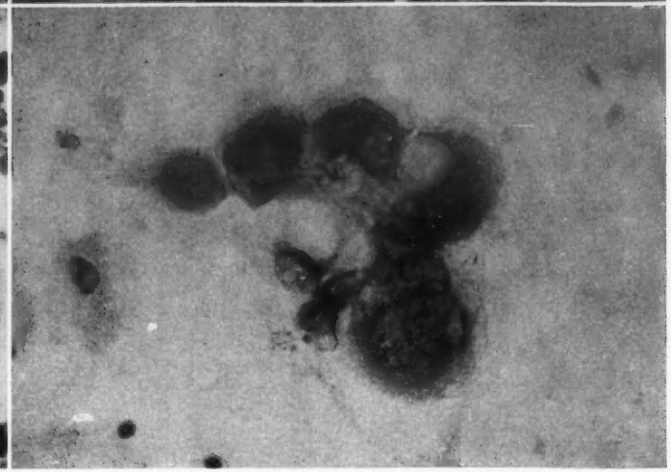

Fig. 1.—Case 1. Primary mucinous adenocarcinoma of the stomach.
Fig. 2.—Case 1. Metastatic adenocarcinoma in the right ovary. Note that some tumor cells contain clear vacuoles.
Fig. 3.—Case 1. The tube was intact but many tumor cells were found free in the lumen.
Fig. 4.—Case 1. Group of adenocarcinoma cells noted in the vaginal smear.

Isbel, Jewett, Allan, and Hertig[10] described the occurrence of tumor cells in the vaginal secretions in a patient suffering from malignant tumor of the urinary bladder, which did not invade the uterus. The tumor was asymptomatic.

From these data, dealing with the cytological diagnosis of extrauterine malignancies, it seems to be quite clear that the correlation between the type of cells and their origin is not definite and that further study with material derived from cases of extrauterine carcinoma is desirable.

Materials and Methods

Cases for this investigation were drawn from the Division of Pathology and Microbiology, University of Tennessee, and the City of Memphis Hospitals. All smears were obtained by aspiration with a pipette introduced into the posterior fornix and were prepared according to the routine Papanicolaou technique. Postmortem cases, including those of newborn infants, were studied cytologically. In addition to these, material was obtained from postpartum patients and patients with pre-eclampsia.

Of 135 cases which were studied, 10 represented various types of extrauterine carcinomas in which the entire genital tract was available for detailed histological examination. Due to the large number of cases involved it was difficult to make an extensive histological study of the uterus in every instance, regardless of the smear findings. For this reason, detailed histological study was carried out only in cases of extrauterine cancers, with approximately 60 blocks prepared from each uterus, at least 5 sections being stained from each block.

Results

A study was made of 10 cases of extrauterine cancer from which the vaginal smears had been taken in the hospital ward or at the autopsy table. The illustrative case histories are as follows.

Report of Cases

CASE 1.—L. R., a 65-year-old Negro woman, was admitted on Dec. 23, 1954, and died on Dec. 31. She complained of weakness and a weight loss of 100 pounds during the 4 months prior to admission. The patient was poorly nourished but not in acute distress. On examination the heart and lungs were not unusual. The abdomen was greatly distended, and a movable mass was palpated in the midline just below the umbilicus. The abdominal fluid could be detected. No gross lesions were observed in the cervix. Masses were noted in the right side of the abdomen and also in the left upper quadrant. The clinical impression was that the patient was suffering from carcinomatosis involving the abdominal viscera.

At necropsy the stomach was found to have a large papillary mass, measuring 12 cm. in diameter, in the prepyloric area and extending through the posterior wall into the region of the pancreas. There was a mass in the right ovarian region which measured 5 cm. in diameter. The remainder of the adnexa were not involved by tumor spread. There were metastases to the liver, peritoneal surface, gall bladder, serosal surface of the large and small intestines, retroperitoneal lymph nodes, both leaves of the diaphragm, and the pancreas. On microscopic examination of the stomach the entire wall was infiltrated by tumor which was relatively well differentiated. Numerous individual cells contained clear vacuoles, causing eccentric nuclear displacement (Fig. 1). The right ovary was extensively replaced by adenocarcinomatous elements. Malignant cells were bulging from the surface capsule which was broken. Many tumor cells contained vacuoles, lending a

Fig. 2.—Case 1. Metastatic [illegible] but many tumor cells were found free in the lumen.
Fig. 3.—Case 1. The tube was intact
Fig. 4.—Case 1. Group of adenocarcinoma cells noted in the vaginal smear.

signet-ring appearance (Fig. 2). Sections of the tube showed well-preserved epithelium around which many tumor cells were seen free in the lumen (Fig. 3). The endometrium and the cervix were not involved.

On examination the smears showed many prominent basal cells among which were a few groups of atypical cells consistent with adenocarcinoma cells (Fig. 4). The nucleoli were large and extremely prominent and stained a deep pink.

Fig. 5.

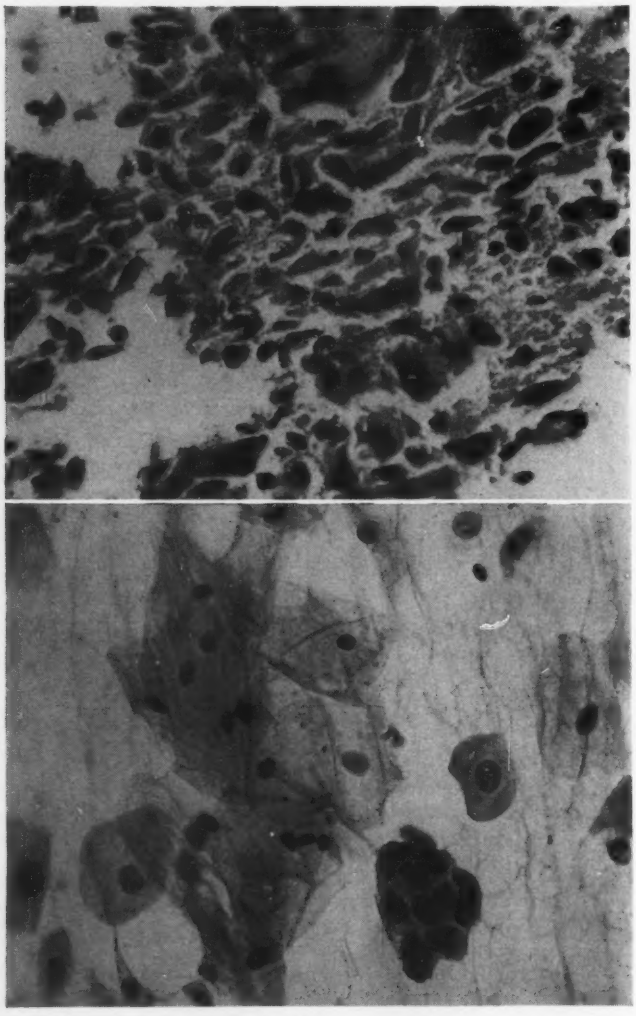

Fig. 6.

Fig. 5.—Case 2. High-power view of tubal lumen disclosed many tumor cells. Primary squamous-cell carcinoma of the anus.

Fig. 6.—Case 2. A group of malignant cells in the smear.

CASE 2.—F. M., a 45-year-old Negro woman, was admitted to the hospital complaining of a cold of a month's duration. This had been associated with a nonproductive cough. Nine months prior to the last admission, the patient had had an abdominal perineal resection for squamous-cell carcinoma of the anus. There had been a 40 pound weight loss in the past 2 months. The physical examination disclosed a temperature of 99.6° F., pulse 104, respiration rate 26, and blood pressure 110/70. The liver extended 5 cm. below

the right costal margin, and there was 1 plus ankle edema noted. The laboratory reports indicated a moderate degree of anemia. Roentgenological examination showed a platelike area of atelectasis in the right lower lobe and an elevated leaf of the diaphragm. Her course was essentially afebrile and rapidly downhill in spite of sustaining therapy. She died on the thirteenth hospital day.

Fig. 7.

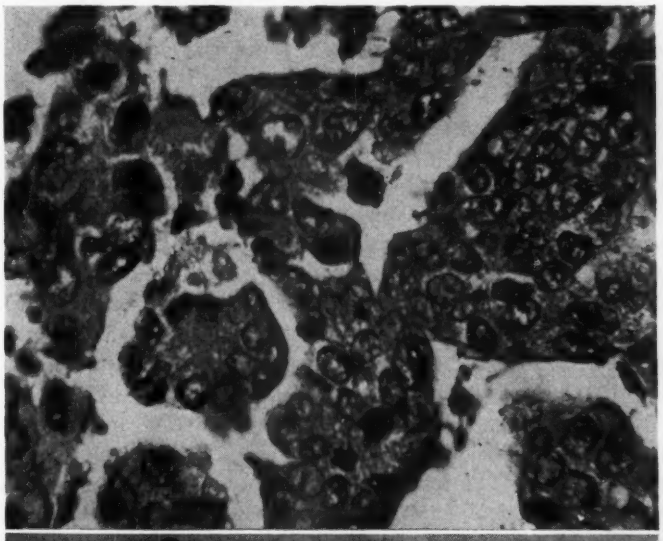

Fig. 8.

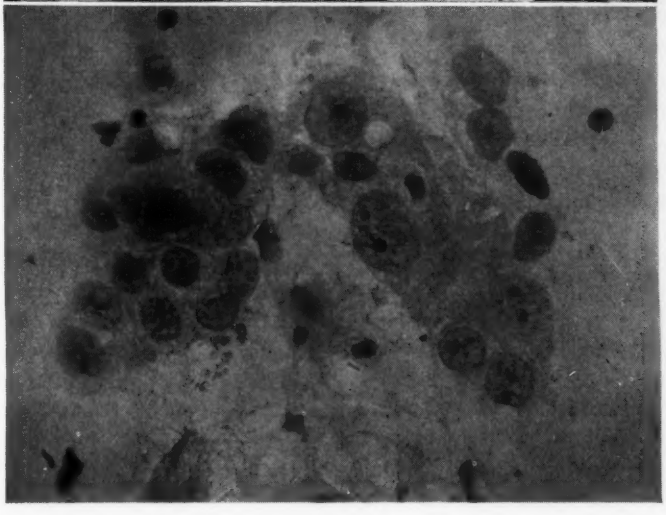

Fig. 7.—Case 3. Adenocarcinoma of left ovary.
Fig. 8.—Case 3. Group of malignant cells found in the smear. Note the prominent nucleoli.

At necropsy the descending colon was found to terminate in a colostomy opening just medial to the left anterior superior iliac spine. The rectum was absent, and the pelvic floor had been peritonized. However, in the left lateral wall of the pelvis, overlying the obturator foramen, was a large, firm mass, 12 cm. in diameter, firmly adherent to the pelvic wall. The lateral view of the tumor showed the dense, firm mass pushing up to the vaginal wall but not penetrating the vagina or uterus. The ureters were not

obstructed. The right fimbria was adherent to the tumor mass. The other tube was free. The celiac, para-aortic, mediastinal nodes, and the thoracic duct were involved by tumor. There were massive involvements of tumor spread in both lungs, the liver, and the nodes.

On microscopic examination the uterus, cervix, and vagina were free from neoplastic growth or invasion. In the tubal lumen there were many extremely large tumor cells (Fig. 5). The ectocervix had an intact squamous epithelium but the submucosa was invaded by tumor. The smears showed a few large, round, dark-staining nuclei with a slight amount of cytoplasm (Fig. 6). Some cells were multinucleated and spindle shaped, with a large amount of cytoplasm. These cells were considered definitely to be atypical and suggestive of undifferentiated carcinoma cells.

CASE 3.—A 67-year-old Negro woman was first seen in the hospital with the chief complaint of painless abdominal distention of 2 weeks' duration. She gave a history of exertional dyspnea of a year's duration. She was gravida xiv, para xii. Vaginal smears were taken and reported as positive for malignant cells. Adenocarcinoma of the endometrium was suspected. On physical examination, however, a firm nodular mass was palpated in the lower umbilical and hypogastric areas. The size of the mass was reported to be approximately 20 by 15 cm. in diameter. Roentgenological examination of the abdomen showed a large density in the pelvis, suggesting either a calcified fibroid or dermoid cyst. An upper gastrointestinal series disclosed no evidence of neoplasm. No abnormality was seen in the colon distal to the hepatic flexure. Biopsies of the endometrium and cervix were negative for malignancy. Sixteen days after admission an exploratory laparotomy and omental biopsy were performed. About 5,000 c.c. of serosanguineous fluid was drained from the peritoneal cavity. The left ovary was not visualized. The tumor growth was noted throughout the peritoneal cavity. The biopsy report on the omental tissue was papillary adenocarcinoma consistent with an ovarian tumor. The patient died 56 days after admission.

Necropsy was performed 3 hours after death. The major findings were limited to the peritoneal cavity where most of the peritoneum, including the omentum and mesentery, contained firm, yellowish-gray tumor nodules. The right ovary appeared to be normal, but the left ovary was extremely enlarged, apparently replaced by tumor. There was also marked enlargement of the uterus due to multiple leiomyomas. There was an endometrial polyp present. The final diagnosis was papillary adenocarcinoma arising from the left ovary extending into the left tube (Fig. 7). The uterus was not involved. There were metastases to the right ovary and most of the abdominal organs. The right tube was also metastasized.

On the smear examinations the basal cells were quite prominent, showing rather deep, pink-stained cytoplasm and dark nuclei. There were the usual number of polymorphonuclear cells as well as the clumps of cervical cells. The endometrial cells were in groups, exhibiting the condensed chromatin network with uniform-sized cellular boundaries. Among these there were groups of cells which were extremely irregular in size and shape, exhibiting sharp nuclear borders with condensed chromatin network. The nucleoli were extremely prominent (Fig. 8).

Comment

It has been postulated by Foot, Wachtel and Plester, Frech, and Papanicolaou and Traut that malignant cells of the ovaries, to appear in the vaginal secretions, must extend through the ovarian capsule and traverse the tube and uterine cavity into the posterior fornix, indicating a far-advanced metastasis to the tubes of the uterus. Furthermore, the ovarian carcinoma can be detected in the smear only when there is metastasis to the tubes or uterus.

However, in our study of 10 cases of extrauterine carcinomas, the uterus was free from neoplastic invasion. Five of these cases had involved the tube, showing continuation of neoplastic growth on the epithelium and submucosa of the tube. In 5 other cases there was no tumor involvement within the tube proper, but many tumor cells were seen free in the lumen. The detailed data are summarized in Tables I and II.

Meigs and associates[11] reported 7 negative cases which were called positive, in which smears showed definite malignant cells but no malignant changes were noted in the uterus. Two of their patients underwent hysterectomy and no cancer was found. There was no explanation for this discrepancy other than the possibility that a small tumor was overlooked at the pathological examination. To avoid this in our study approximately 60 blocks were prepared from each uterus, regardless of gross appearance. No gross and microscopic evidence for neoplastic growth was obtained in 10 cases of extrauterine carcinomas.

TABLE I. EXTRAUTERINE CARCINOMAS INVOLVING THE FALLOPIAN TUBES

AGE	RACE	PRIMARY LESION	DURATION	SMEARS	TUBAL INVOLVEMENT
53	Negro	Serous cystadenocarcinoma of left ovary	6 weeks	Positive	Left tube
67	Negro	Papillary adenocarcinoma of left ovary	2 months	Positive	Both tubes
82	White	Adenocarcinoma of right ovary	?	Positive	Right tube
48	Negro	Adenocarcinoma of left ovary	3 weeks	Positive	Left tube
*72	White	Adenocarcinoma of right tube	?	Positive	Right tube

*A detailed case report was presented in AM. J. OBST. & GYNEC., Vol. 70, No. 1, on page 29.

TABLE II. EXTRAUTERINE CARCINOMAS WITHOUT METASTASES TO THE FALLOPIAN TUBES BUT MALIGNANT CELLS FOUND IN THE LUMEN OF THE TUBES

AGE	RACE	PRIMARY LESION	DURATION	SMEARS	PERITONEAL FLUID
48	Negro	Carcinoma of right breast	16 years	Positive	Present
23	Negro	Adenocarcinoma of stomach	6 months	Positive	Present. Both ovaries involved
65	Negro	Adenocarcinoma of stomach	4 months	Positive	Present. Right ovary involved
45	Negro	Squamous-cell carcinoma of anus	9 months	Positive	No ascites
54	White	Carcinoma of left kidney	25 months	Positive	Present

No significant cytological alterations were noted on the vaginal smears of 125 miscellaneous patients representing various kinds of diseases such as Albright's syndrome, eclampsia and tuboovarian abscess, with rupture.

According to Papanicolaou and Traut, the cytology of metastatic cystadenocarcinoma of the ovary is most often sufficiently characteristic to permit identification; the nucleoli are more prominent than are those in cells seen in cases of uterine cancer. However, on the basis of our present study, it seems to be extremely difficult to determine the origin of the tumor by a few malignant cells in the vaginal smears.

Summary

Malignant cells were found in the vaginal smears in 10 cases of extrauterine carcinoma whose primary sites were breast, stomach with involvement of ovary, anus, kidney, ovaries, and Fallopian tube. Examination of the uteri and cervices failed to show any evidence of primary or metastatic tumor. No significant gynecological complaints were ever mentioned by these patients. In the cases which did not involve the tube many tumor cells were seen free in the lumen of the tube. On the smears tumor cells were seen in clusters in many instances, although a scanty number of cells were noted in some smears.

From our investigation, it seems to be quite obvious that well-preserved tumor cells can be carried into the tube by direct extension, from metastatic tumor to the ovary or tube, by ascitic fluid which contains tumor cells, or by ameboid movement of cells themselves. These cells may be carried through the lumen of the tube by peristalsis or ciliary movements of the epithelium of the Fallopian tube, and travel through the uterine cavity to appear in the vaginal pool where these cells might be picked up and recognized as cancer cells.

At the present stage we are not able to establish any distinct possibility of making diagnosis of extrauterine carcinomas by means of vaginal smears. In other words, it would be extremely difficult to determine the exact primary site of the tumor on the basis of smear findings alone. However, if the cytological diagnosis of Class 4 or 5 is made on the vaginal smears, and multiple biopsies of the uterus and cervix do not show any malignant change, then one certainly should consider the distinct possibility of primary extrauterine carcinomas, since such tumors may often be asymptomatic.

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COMPARATIVE RESULTS OF THE ROUTINE PAPANICOLAOU AND THE DRAGHI TAMPON CYTOLOGIC STUDIES IN ATYPICAL HYPERPLASIA OF THE CERVIX AND UTERINE CANCER

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THE purpose of this study is to evaluate the Draghi tampon as a method of collecting a cellular specimen from the uterine cervix by comparing the results with the routine method of aspiration and scraping the cervix and with the histopathologic findings.

Cytology material obtained by aspiration of the cervical canal plus scraping the cervix about the os have given us a comprehensive cellular sample of this region. Such studies have become a routine part of any pelvic examination. The material obtained from the posterior vaginal fornix alone or from scraping the visible cervix alone has not been as satisfactory; probably the reason for this is our finding that the major epithelial alteration is within the cervical canal in 90 per cent of the instances.

It is our conviction that ideally cytology studies and biopsies should be *a part of and not a substitute for* a thorough pelvic examination. Yet it is admitted that a simple method of mass screening by the cellular technique would be utilized by a large group of women unwilling to submit to periodic pelvic examinations and would help in the detection of early uterine cancer. Techniques of mass screening have been tried; the newest techniques utilizing special vaginal tampons have been reported by Brunschwig, Papanicolaou, Thornton, and Nieburgs.

Materials and Methods

An evaluation of the Draghi tampon* method was made on the inpatients admitted to the Gynecology Service at MacDonald House. Since most of these patients had had recent cellular studies of specimens obtained by aspiration and scraping of the uterine cervix, there was an opportunity to correlate the results of the two techniques with the histologic findings.

Eight hundred and twenty-seven unselected admissions to the Gynecology Service were studied from Dec. 8, 1954, to Sept. 2, 1955, and from this latter date until Feb. 16, 1956, an additional 21 selected patients were studied, making a total of 848 patients. The majority of the patients had cervical canal aspirations and scrapings prior to admission (an average of two to four weeks).

The Draghi detection tampon consists of a tightly compressed cylinder of cotton with a central core and wick; the distal (or cervical approximating) portion of this cylinder is encased in a sheath of nylon with a fine mesh. In

*The special Draghi tampons used in this study were supplied by Tampax, Inc., Palmer, Mass.

turn the cotton cylinder is enclosed within a divided cardboard container which aids insertion by its plunger action. The group of 827 patients had a tampon inserted by the graduate nurse on duty the evening before operation and it was removed by the operating room nurse immediately prior to the operation. A few patients not included in this series refused to have the tampon inserted or could not retain it because of relaxation or prolapse. Thus the tampons remained in the vagina for 12 to 16 hours. Upon removal the nylon-encased end was pressed (tip or tip and sides) in sequence upon three clean glass slides which were immediately fixed in alcohol and ether. An additional group of 21 selected patients (i.e., mainly patients with known changes by the regular cytologic technique) had the tampon inserted in the operating room only a few minutes before the contemplated surgical procedure.

For this study slides prepared by the Draghi tampon technique were reported as negative, suspicious, or positive. Although many specimens were not entirely satisfactory they were classified in one of the three listed categories.

Results

The histologic studies were used as the final determinant. The results in the groups with microscopically proved atypical hyperplasia, carcinoma in situ, invasive squamous-cell cancer, and endometrial adenocarcinoma are shown in Table I.

TABLE I. COMPARATIVE RESULTS IN NUMBERS

HISTOPATHOLOGY	TOTAL NUMBER	ROUTINE AVAILABLE	CYTOLOGY POSITIVE OR SUSPICIOUS	DRAGHI AVAILABLE	CYTOLOGY POSITIVE OR SUSPICIOUS
Atypical hyperplasia	20	19	15	20	2
Carcinoma in situ	13	12	12	13	6
Invasive cancer	27	17	16	27	24
Endometrial cancer	16	13	6	16	11
Total	76	61	49	76	43

Although the groups were limited in number, it seems that the Draghi tampon method compares unfavorably with the regular cytology in the presence of atypical hyperplasia or carcinoma in situ of the cervix. The two methods are of about equal value in detecting invasive cancer; the Draghi method may be better than regular cytology with endometrial cancer because of the overnight exfoliation. The results with regular cytology in this small group of patients with endometrial cancer is not as good as in our previous series, i.e., less than half positive as compared to about three out of four.

A group of 12 patients had changes by one or both cytologic techniques without histologic confirmation. The group is still under study and it is probably significant that 5 of the 12 had previous irradiation treatment for cancer of the cervix.

An additional group of 760 patients were studied; these all had negative Draghi tampon reports and benign tissue studies. In most instances previous routine cytology reports were available and when available they were negative.

Comment

Papanicolaou and Brunschwig made the first reports of the Draghi tampon technique. Brunschwig reported 52 positives out of 65 patients with untreated cancer of the cervix and an additional 11 "deferred readings"; thus the "recall signal" was 63 out of 65 instances. Also 18 out of 130 patients without

Fig. 1.

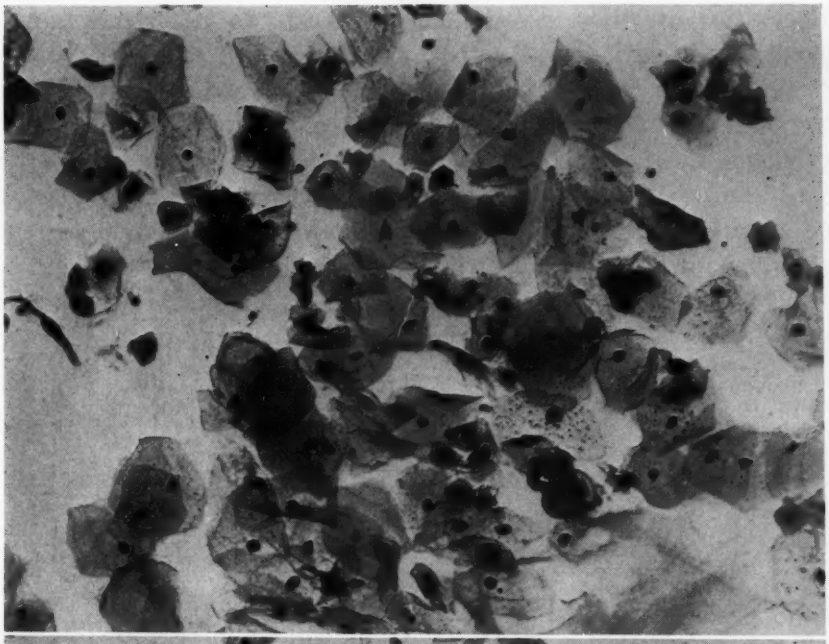

Fig. 2.

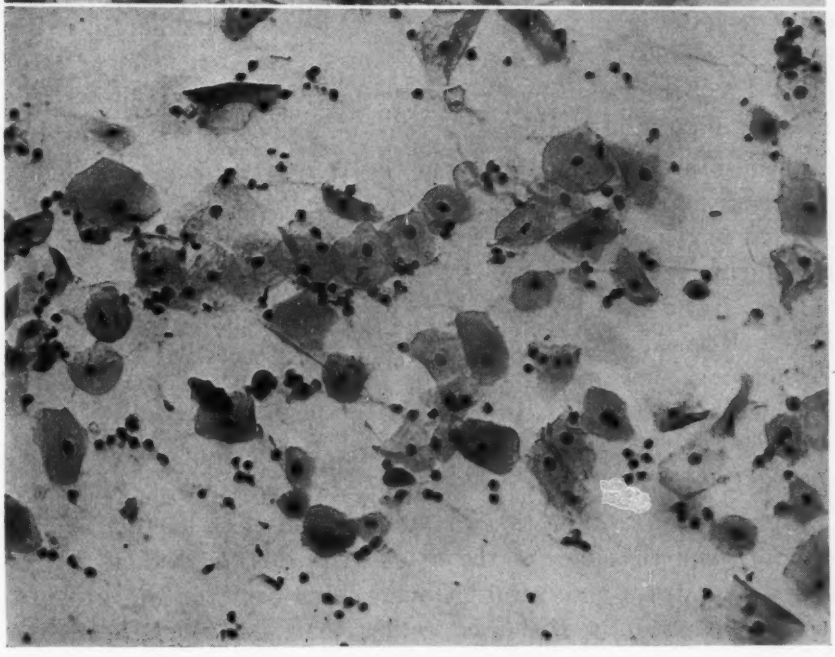

Fig. 1.—J. G., No. 497-890. Cellular study obtained by aspiration of the cervical canal. Read as "cells compatible with atypical hyperplasia" and histologic studies showed atypical hyperplasia. (×200.)

Fig. 2.—J. G., No. 497-890. Same patient as Fig. 1. Cellular study obtained by Draghi tampon method. Read as "negative." (×200.)

known cancer had "deferred" readings. Papanicolaou stated, "In general, the smears were satisfactory from the point of view of quality of secretion and preservation of cells . . ." and he felt that the material was more free of decayed cells, bacteria, and detritus than the material obtained by aspiration of the vaginal pool. Thornton reported on 2,059 patients screened by this technique; 147 of this group had dilatation and curettage and/or biopsy of the cervix and there was correlation of the biopsy and the cytology in 133, or 90.5 per cent. Eleven of the instances in Thornton's series which showed negative cytology and "positive" biopsies were summarized in case reports: 3 had carcinoma in situ, 2 endometrial adenocarcinoma, one a metastatic adenocarcinoma in the vagina, 4 an invasive cancer of the cervix (2 with previous irradiation treatment), and one treated invasive cancer of the cervix in which the biopsy was very questionable. It is worthy of emphasis that the 3 carcinomas in situ which had negative Draghi tampon smears were the only in situ cancers of the entire series.

Nieburgs employed a slightly modified tampon technique in which the upper half of the tampon was replaced by a nylon sponge and this nylon sponge was drawn through a special box with glass slides at the top and bottom. He compared the results in the sample group with endocervical swab smears and previous biopsies or biopsies at the time. The tampon was left in place for four hours in 15 patients and for 24 hours in another 15 patients. He found perfect correlation between the biopsies and the sponge smear; in 2 instances the endocervical smear gave a false negative. These 30 patients all had biopsy reports of dysplasia, borderline lesions, or carcinoma in situ.

Our results indicate that by using the Draghi tampon technique invasive cancer and endometrial adenocarcinoma could be detected with a facility approximately equal to the cervical aspiration and scraping technique, but carcinoma in situ and particularly atypical hyperplasia (i.e., dysplasia) of the uterine cervix (Figs. 1 and 2) were not even suspected in a high percentage of the Draghi tampon specimens. The group with minimal changes, no gross lesions, and no symptoms must be suspected by any mass detection technique if this method aims to take full advantage of cytology and preventive medicine. Anything short of this compounds the errors already inherent in the lack of a complete pelvic examination.

It is possible that alterations of the time-in-place factor, length of the tampon, width and character of the nylon mesh, or the method of transfer to the slides would prove successful in overcoming some of the problems. The nylon sponge as used by Nieburgs, rather than the nylon mesh, may be a marked improvement.

Summary

1. The Draghi detection tampon technique was compared with the regular cytologic studies by endocervical aspiration and scraping in a group of gynecologic patients. Histologic specimens were available in every instance.

2. Seven hundred and sixty patients had negative cytology by the Draghi tampon method and negative histologic studies. The majority of these had previous routine cytology studies and all studied were negative.

3. Seventy-six patients had atypical hyperplasia, carcinoma in situ invasive cancer, or endometrial adenocarcinoma.

A. Of 20 patients with atypical hyperplasia, 19 had had previous routine cytology and 15 of these specimens were suspicious or positive; only 2 of the 20 had suspicious Draghi tampon specimens.

B. Of 13 patients with carcinoma in situ, 12 had had previous routine cytology and all of these were suspicious or positive; only 6 of 13 had suspicious or positive Draghi tampon specimens.

C. Twenty-seven patients had invasive cancer. Sixteen of the 17 studied by routine cytology were suspicious or positive, while 24 of the 27 were suspicious or positive by the Draghi tampon method.

D. Sixteen patients had endometrial adenocarcinoma. Six of the 13 studied by routine cytology were suspicious or positive, while 11 of the 16 were suspicious or positive by the Draghi tampon method.

E. Twelve patients had changes by routine and/or Draghi cytologic studies but histologic proof was lacking. Five of these were from patients with cancer of the cervix treated by irradiation.

4. Comparatively the Draghi tampon method was not satisfactory in detecting the majority of atypical hyperplasia and carcinoma in situ lesions of the cervix, but it was about as satisfactory as the routine cytology when dealing with invasive cancer and possibly more so when the lesion was endometrial adenocarcinoma.

5. Any mass detection technique generally compromises the many advantages of a thorough pelvic examination. The methods used must not compound this by failure to utilize cytologic techniques to their fullest advantage.

6. Possibly alterations in the Draghi tampon, the length of the retention, or the methods of transfer to the glass slides will increase the reliability of this method.

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THE USE OF INTERSTITIAL RADIOACTIVE COBALT NEEDLES IN THE TREATMENT OF CARCINOMA OF THE CERVIX

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THE use of radioactive cobalt in the treatment of cancer was first proposed by Meyers.[1] Working at the Ohio State University College of Medicine, Meyers developed radioactive isotope cobalt^{60}. Barnes[2] reported the initial study of the application of radioactive cobalt in the form of interstitial needles. This present communication is an analysis of the five-year survival figures of 99 patients treated with cobalt^{60} interstitial needles for carcinoma of the cervix.

Source of Material

The radioactive cobalt supplied for this study was obtained by Meyers from the Division of Biology and Medicine of the Atomic Energy Commission. Cobalt^{60} is activated in the Oak Ridge Nuclear Reactor (Pile). The properties of cobalt^{60} which allow its application in the treatment of cancer have been reviewed by Meyers.[3]

1. After activation in a nuclear reactor, cobalt^{60} has a half life of 5.3 years, making it relatively stable.
2. It has a soft beta radiation which is easily filtered out.
3. The gamma radiation is homogenous—1.17 and 1.33 million electron volts (Mev).
4. The strength of any given lot of the material is determinable prior to irradiation in the pile. Two pieces of cobalt of identical weight and size when exposed to the reactor for different lengths of time will have different intensities when activated, and such values can be calculated ahead of time.
5. Residual activity can be "warmed up" in the reactor.
6. There are no gaseous radioactive daughters, leakage is impossible, and the regrouping of units of activity is facilitated.
7. After activation cobalt remains magnetic, which also facilitates handling. A long rod with a controllable magnet at the end is used for transferring the material and for loading the needles. This provides additional safety for those who handle the radioactive material.
8. Cobalt^{60} can be activated in any desired shape and form, and in any desired quantity at a moderate cost.
9. Suitable alloys can be found which are chemically inert, inexpensive, and easily machined. The alloying material can be so selected that it is not necessarily activated by the nuclear reactor.

The essential fact for the clinician using cobalt^{60} is that it supplies a good source of gamma radiation which can be readily controlled with proper safety measures.

Source of Patients

This study was carried out at the Ohio State University College of Medicine, Gynecologic Tumor Clinic. The patients are a segment of 99 out of a total of 1,217 patients being followed at the Gynecologic Tumor Clinic, as of Jan. 1, 1956. Of the total number of patients, one is untraced. All other patients have been followed since their registration. There are no other "lost" patients. The single patient untraced is not in the series treated with radioactive cobalt^{60} needles. The series treated by the needle technique is comprised of both clinic and private patients who have registered through the Gynecologic Tumor Clinic.

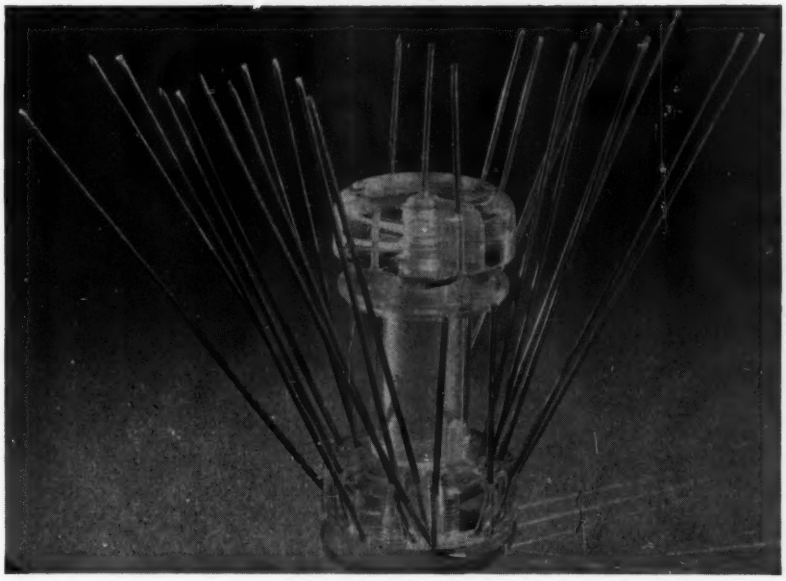

Fig. 1.—Basic pattern.

Procedure

Between October, 1948, and November, 1951, 99 patients were treated by the interstitial needle technique. The radioactive cobalt^{60} was prepared from pure cobalt metal. In the latter form it was submitted for activation as 0.3 cm. lengths of 0.508 mm. diameter wire. After activation, these cylinders were placed in stainless steel needles using inert aluminum cylinders between to distribute the linear intensity as desired. Fig. 1 shows the basic patterns evolved. To compensate for the decreased amount of gamma radiation at the area of needle divergence the distal portion of the needles was given a heavier load. Fig. 2 shows a roentgenogram of typical pattern in situ. To increase the accuracy of needle implant, Lucite templates were made containing brackets of previously drilled guide holes. The needles were then thrust through these templates so that uniform patterns could be obtained. The fundamental plan of irradiation was to furnish a dosage of 6,000 to 7,000 tissue roentgens to the tumor by means of cobalt^{60} gamma radiation. This was supplemented by external therapy from x-irradiation. An average of 2,000 r to a 20 by 20 cm. anterior port and posterior port was given.

Eighteen of the 99 patients in the cobalt needles series had prior or supplemental therapy. There were 8 patients in Clinical Stage II and 10 patients in Clinical Stage III who had combined therapy. Those patients in Stages I and IV had only the cobalt needle therapy. The patients who had prior therapy were those who received central radium. Supplemental therapy was given in the form of radioactive cobalt colpostat and tandem. It was given in instances of recurrence of tumor growth. The amount of therapy over and above the cobalt needle therapy is listed by clinical stage in Tables I and II. The total irradiation to point A is given in roentgens. Complications are listed with the type of application.

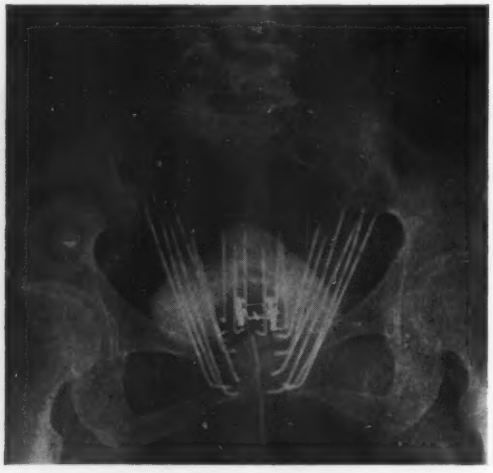

Fig. 2.—Roentgenogram of typical pattern in situ.

TABLE I. LIST OF COMBINED THERAPY PATIENTS, STAGE II

DOSAGE	COMPLICATIONS
Cobalt Colpostat and Tandem (Roentgens to Point A).—	
1. 4,000 r	
2. 6,400 r	
3. 6,900 r	
4. 1,800 r	Duodenal obstruction and jaundice
Radium.—	
1. 7,000 r	Rectovaginal fistula
2. 6,200 r	
3. 10,000 r	
4. 6,200 r	

TABLE II. LIST OF COMBINED THERAPY PATIENTS. STAGE III

RADIUM (ROENTGENS TO POINT A)	COMPLICATIONS
1. 4,800 r	
2. 7,100 r	Vesicovaginal fistula
3. 2,200 r	Rectovaginal fistula and colostomy
4. 6,200 r	
5. 2,600 r	
6. 5,300 r	
7. 7,800 r	Vesicovaginal and rectovaginal fistula
8. 6,000 r	Bowel obstruction (large)
9. 6,200 r	Rectovaginal fistula
10. 8,000 r	

Results

The five-year survival rates are indicated in Table III. This table is arranged in League of Nations Classifications I through IV. They are summarized by year of registration and list total survivors by year.

TABLE III. PATIENTS WHO RECEIVED COBALT60 NEEDLES BY YEAR OF REGISTRATION

YEAR	NO.	1	2	3	4	5	6	7	8
Stage I.—									
1948	0	0	0	0	0	0	0	0	0
1949	0	0	0	0	0	0	0	0	
1950	3	3	2	2	2	2	2		
1951	0	0	0	0	0	0			
1952	0	0	0	0	0				
1953	0	0	0	0					
1954	0	0	0						
1955	0	0							
Survivorship in years and by percentage	3	3 of 3	2 of 3	2 of 3	2 of 3	2 of 3	2 of 3	0	0
			66.7	66.7	66.7	66.7	66.7		
Stage II.—									
1948	3	1	1	1	0	0	0	0	0
1949	8	6	3	3	3	3	3	3	
1950	15	11	11	8	8	8	8		
1951	9	8	7	7	7	6			
1952	0	0	0	0	0				
1953	0	0	0	0					
1954	0	0	0						
1955	0	0							
Survivorship in years and by percentage	35	26 of 35	22 of 35	19 of 35	18 of 35	17 of 35	11 of 26	3 of 11	0
		74.2	62.9	54.2	51.4	48.6	42.3	27.2	
Stage III.—									
1948	4	3	2	2	1	1	1	1	1
1949	12	10	8	5	4	4	4	4	
1950	27	23	9	7	7	7	6		
1951	7	7	2	1	1	1			
1952	0	0	0	0	0				
1953	0	0	0	0					
1954	0	0	0						
1955	0	0							
Survivorship in years and by percentage	50	43 of 50	21 of 50	15 of 50	13 of 50	13 of 50	11 of 43	5 of 16	1 of 4
		86.0	42.0	30.0	26.0	26.0	25.5	31.2	25.0
Stage IV.—									
1948	0	0	0	0	0	0	0	0	0
1949	4	4	1	0	0	0	0	0	0
1950	5	4	3	1	1	0	0		
1951	2	1	1	1	1	1			
1952	0	0	0	0	0				
1953	0	0	0	0					
1954	0	0	0						
1955	0	0							
Survivorship in years and by percentage	11	9 of 11	5 of 11	2 of 11	2 of 11	1 of 11	0 of 9	0 of 4	0
		81.8	45.5	18.1	18.1	09.0	—	—	

There were 3 patients with Stage I tumors. Two of the 3 lived five years. There were 35 patients with Stage II tumors. Seventeen, or 48.6 per cent, lived five years. There were 50 patients with Stage III tumors. Thirteen, 26 per cent, of these patients lived for five years. There were 11 Stage IV patients. One, 9 per cent, of these patients lived for five years.

Complications

Proctitis after interstitial needle radiation was uniform. The onset of this complication began seven to thirty days after removal of the needles. The patient first experienced nausea and anorexia. This was followed by a variable amount of tenesmus and diarrhea. There was gross rectal bleeding recorded on 43 patients' charts. The symptomatology was best controlled by use of Kaopectate and/or paregoric, low-residue diet with boiled skim milk three times daily, belladonna-opium rectal suppositories, and antibiotics routinely administered. In patients who had a drop in hemoglobin below 9 Gm., whole blood transfusions were given.

The severe complications were as follows: rectovaginal fistulas 11, vesicovaginal fistulas 6, ureteral obstruction requiring transplant 1, large bowel obstruction requiring colostomy 11, and small bowel obstruction 1.

TABLE IV. SEVERE COMPLICATIONS BY STAGE

STAGE	RECTOVAGINAL FISTULA	VESICOVAGINAL FISTULA	LARGE BOWEL OBSTRUCTION	SMALL BOWEL OBSTRUCTION	TOTAL
I					0
II	2	1	4	1	8
III	8	3	6		17
IV	1	2	1		4
Total	11	6	11	1	29

Summary

1. Analysis of five-year survivorship in 99 patients with carcinoma of the cervix treated with radioactive cobalt needles has been made:

In Stage I, 2 of 3 patients lived 5 years (66.7 per cent).

In Stage II, 17 of 35 patients lived 5 years (48.6 per cent).

In Stage III, 13 of 50 patients lived 5 years (26.0 per cent).

In Stage IV, 1 of 11 patients lived 5 years (9.0 per cent).

2. Forty-three of the 99 patients developed radiation proctitis to the extent of gross rectal bleeding.

3. Severe complications include 11 rectovaginal fistulas, 6 vesicovaginal fistulas, 11 large bowel obstructions, 1 small bowel obstruction. There were 2 patients with large bowel obstruction who refused colostomy and died.

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AN EXPERIMENTAL STUDY OF URETERAL INJURIES IN RADICAL PELVIC SURGERY*

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THE revival of interest in radical surgery for the treatment of pelvic malignancies has stimulated this investigation of injuries of the renal tract. The problem of ureterovaginal fistula is perhaps the most serious complication encountered in radical pelvic surgery. Although Knaus,[3] Pratt,[6] and Yagi[9] have had a very low, 2 to 4 per cent, incidence of fistula, Douglas,[2] St. Martin,[8] and Liu and Meigs[5] have reported figures ranging from 7 to 18 per cent. Such a difference might be considered as a reflection of the skill of the various surgeons. However, it may well be an indication of the extent of the surgical procedure, the stage of the disease, the status of the patient, and numerous other factors. The avoidance of trauma, the preservation of blood supply, and the need of peritonization are among the many suggestions that have been offered for the prevention of ureteral fistulas. Little did Sampson[7] realize the future significance of his statement made in 1904 that "the most serious complication, which has been associated with the advance in the operative treatment of carcinoma cervix uterus, has been that of injury to ureter."

One of the earliest studies in the field of ureteral injuries was carried out by Sampson in 1904. The hysterectomies for carcinoma of the cervix at The Johns Hopkins Hospital for the years 1889 through 1904 had been associated with a 12 per cent incidence of ureterovaginal fistula. As the result of his experiments in dogs, Sampson concluded that the ureter could be dissected free for its entire length without necrosis occurring, as long as the periureteral arterial plexus was not sufficiently injured. In addition, he believed that the formation of adhesions about the isolated ureter was important for protection and as a source of secondary blood supply. The replacement of surgery by radiation in the treatment of uterine malignancy during the following years largely eliminated the problem of ureteral necrosis. By and large, further research in this field remained at a standstill.

As previously mentioned, the preservation of blood supply has been widely stressed in the prevention of ureteral fistula. And yet, the radical hysterectomy performed by us includes routine isolation of the ureters from all of the surrounding tissue and blood vessels as well as a bilateral ligation of the hypogastric arteries. Over the past five years, such a complete dissection has been associated with an incidence of ureteral fistula of 7 to 12 per cent. If the meticulous preservation of one or more particular vessels was essential, one should anticipate a higher incidence in our clinic. The current concept of the

*Presented at a meeting of the New York Obstetrical Society, Dec. 13, 1955.

blood supply of the human ureter was well demonstrated by Daniel and Shackman.[1] They showed in a study of 100 ureters, that 88 received branches from the renal and uterine or vesical arteries. In addition, these 88 ureters received 1 to 3 long arteries from the aorta, ovarian, common iliac, or hypogastric arteries for the intermediate portion of the ureter. Twelve ureters received branches from the renal and uterine or vesical arteries but only minute peritoneal twigs for the intermediate portion. In the case of 2 ureters, there were no branches from the renal, uterine, or vesical arteries, instead only long arteries to the intermediate portion. In addition, these same authors were impressed by the asymmetry of the blood supply in each cadaver studied.

Fig. 1.—Illustrates the circulatory embarrassment of the bladder and terminal portions of the ureters following complete isolation of both ureters, ligation of their blood supply, and the hypogastric arteries.

With this as a background, we undertook to evaluate in dogs the following factors that might be contributing to the development of ureterovaginal fistulas following radical hysterectomy and pelvic lymph node dissections: (1) blood

supply, (2) trauma, (3) peritonization, (4) infection, (5) radiation, (6) a combination of one or more of the preceding.

In the first series of 5 dogs (Group A), each animal was prepared and draped under Nembutal anesthesia. The abdomen was opened via a suprapubic midline incision. Both ureters were meticulously isolated and their blood supply completely dissected and ligated. The hypogastric arteries were bilaterally ligated. As will be noted in Fig. 1, the terminal portion of the ureter and bladder were markedly discolored and showed evidence of vascular embarrassment at the conclusion of the dissection. The ureter of the left side was then reposited and carefully reperitonized. On the right side, the ureter was allowed to drop freely into the pelvis and occupy whatever position it might find. The abdomen was closed in layers. Between the tenth and twelfth postoperative days, the animal was sacrificed and an autopsy performed. In Table I, the findings in this group are recorded.

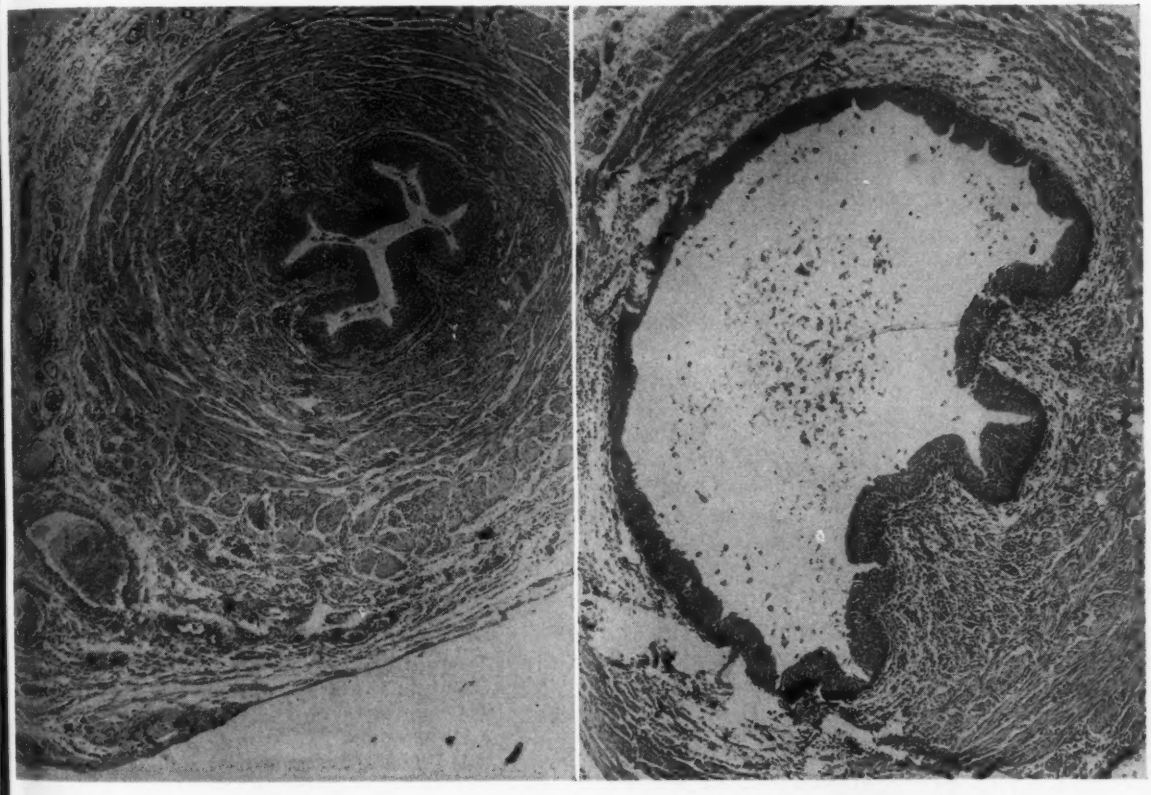

Fig. 2. Fig. 3.

Fig. 2.—Microscopic section of normal right ureter from Animal A-1.
Fig. 3.—Microscopic section of dilated left ureter from Animal A-1.

No fistulas were produced. In 3 animals, the peritonized ureter was found to be associated with hydroureter and hydronephrosis as well as infection. In 2 animals, the unperitonized ureter was associated with hydroureter and hydronephrosis plus infection. In Fig. 2, the microscopic section of the normal right ureter of animal A-1 is seen. The vessels of the periureteral plexus may be seen at the periphery. In Fig. 3, the left ureter in the same animal is noted to be dilated, thick walled, and infected.

In the second series of dogs (Group B), an attempt was made to evaluate the factor of trauma. Following the isolation of both ureters and the ligation of their blood supply, the ureters were intentionally traumatized by clamping, rubbing with gauze, picking up with forceps, retraction, etc. Both hypogastric arteries were ligated. Upon repositing the ureters, a gauze pack was placed down along the right ureter and brought out through the abdominal incision. No attempt was made at reperitonization. Between the tenth and twelfth postoperative days the animal was sacrificed and autopsied. As noted in Table II, animal B-1 died on the first postoperative day and was found to have a necrotizing peritonitis with bilateral hydroureter and hydronephrosis, but no evidence of fistula.

TABLE I. GROUP A. BILATERAL ISOLATION OF THE URETERS AND LIGATION OF THEIR BLOOD SUPPLY. RIGHT URETER LEFT FREE; LEFT URETER REPERITONIZED

DOG NO.	RIGHT SIDE			LEFT SIDE		
	DILATATION	INFECTION	FISTULA	DILATATION	INFECTION	FISTULA
1	0	0	0	+	+	0
2	0	0	0	0	+	0
3	+	+	0	+	+	0
4	0	0	0	+	+	0
5	+	+	0	0	0	0

TABLE II. GROUP B. BILATERAL TRAUMATIC ISOLATION OF THE URETERS AND LIGATION OF THEIR BLOOD SUPPLY. URETERS WERE NOT REPERITONIZED

DOG NO.	RIGHT SIDE			LEFT SIDE			
	DILATATION	INFECTION	FISTULA	DILATATION	INFECTION	FISTULA	
1	+	+	0	+	+	0	(Died first postoperative day)
2	0	+	0	0	0	0	
3	0	0	0	+	0	0	
4	0	0	0	0	+	0	
5	0	+	0	0	0	0	

There were no fistulas produced in any of the remaining animals in this series. One animal showed hydroureter and hydronephrosis without any evidence of infection. In Fig. 4, microscopic sections of the left ureter from animal B-2 show a thin-walled ureter with considerable fragmentation of the muscularis, but no evidence of infection or hydroureter.

In the third series of dogs (Group C), the same operative procedure was carried out as in Group A. In addition, the right ureters were enveloped in polyethylene tubing to prevent the development of adhesions. In the first two groups studied, the findings at autopsy suggested that these adhesions might have played a significant role in protecting the ureter and introducing additional blood supply. Such a possibility had originally been proffered by Sampson as a result of his studies in dogs. However, the autopsy findings seen in Table III would not bear this out.

TABLE III. GROUP C. BILATERAL ISOLATION OF THE URETERS AND LIGATION OF THEIR BLOOD SUPPLY. RIGHT URETER PROTECTED WITH POLYETHYLENE. LEFT URETER LEFT FREE

DOG NO.	RIGHT SIDE			LEFT SIDE			
	DILATATION	INFECTION	FISTULA	DILATATION	INFECTION	FISTULA	
1	+	0	0	0	0	0	
2	+	+	0	+	0	0	(Died third postoperative day)
3	+	0	0	0	0	0	
4	0	0	0	0	+	0	
5	+	0	0	+	+	0	

No fistulas were produced. The fact that 4 of the 5 ureters that had been enveloped by polyethylene tubing, showed hydroureter and hydronephrosis without evidence of infection suggests that the tubing may shield the ureter from extrinsic infection, but at the same time produce dilatation through some mechanical means. In Fig. 5, the right ureter from animal C-1 shows considerable dilatation and fragmentation of the walls without any evidence of infection.

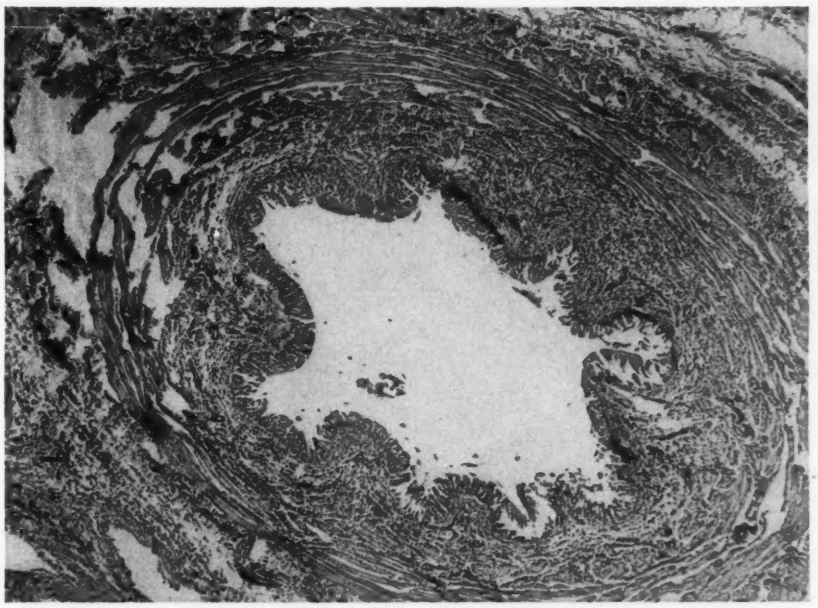

Fig. 4.—Microscopic section of left ureter from Animal B-2 discloses considerable fragmentation of the muscularis.

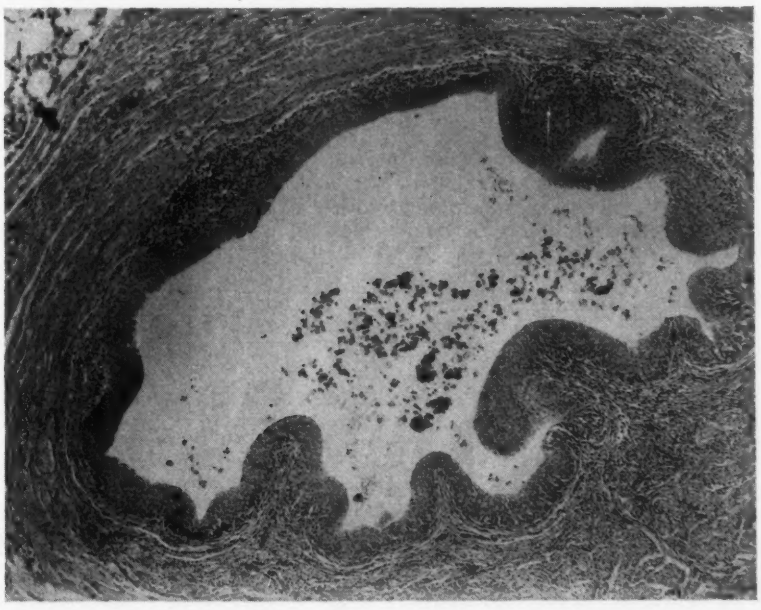

Fig. 5.—Microscopic section of the right ureter from Animal C-1 reveals marked dilatation of the lumen.

The fourth series of dogs (Group D) were employed to study the organisms most commonly found in the postoperative urinary tract infection among the radical hysterectomy patients. They are: *Bacillus proteus, Escherichia coli,* and *Aerobacter aerogenes.* In this group, following the usual isolation of the ureters and the ligation of the blood supply, the left ureter was inoculated with a pure culture of one of the above organisms and then peritonized. As recorded in Table IV, 2 dogs, which had been infected with *B. proteus* succumbed to generalized sepsis within twenty-four to forty-eight hours. Both had marked hydroureter, hydronephrosis, and infection. In the case of the ureter inoculated with *Aerobacter aerogenes,* a ureteral fistula was produced. This represented the first in the entire study up to that point. All of the inoculated ureters showed dilatation and infection. In Fig. 6, the left ureter from animal D-2 shows considerable thickening of the wall in association with mild infection.

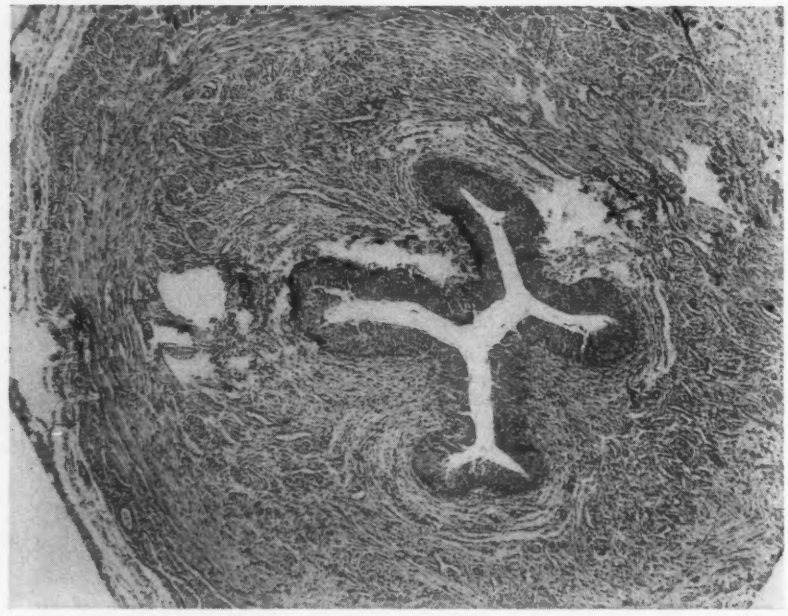

Fig. 6.—Microscopic section of the left ureter from Animal D-2 shows considerable thickening of the wall. The lumen is contracted in this area.

TABLE IV. GROUP D. BILATERAL ISOLATION OF THE URETERS AND LIGATION OF THEIR BLOOD SUPPLY. LEFT URETER INOCULATED WITH SPECIFIC ORGANISMS AND REPERITONIZED

DOG NO.	BACTERIA AND SIDE	RIGHT SIDE			LEFT SIDE		
		DILATATION	INFECTION	FISTULA	DILATATION	INFECTION	FISTULA
1	*B. proteus* (B)	+	+	0	+	+	0 (Died first postoperative day)
2	*E. coli* (L)	0	0	0	+	+	0
3	*B. proteus* (R)	+	+	0	+	+	0
4	*A. aerogenes* (L)	0	0	0	+	+	+
5	*B. proteus* (L)	+	+	0	+	+	0 (Died second postoperative day)

In the final series (Group X-ray), 4 dogs were selected and administered a complete pelvic course of deep x-ray therapy. The dosage was equivalent to that administered to humans in the treatment of uterine malignancy. A 400

kv. unit was employed. A depth dose at the lateral pelvic wall of 3,267 to 3,815 r. was given via anterior and posterior pelvic ports measuring 6 by 9 cm. Eight to twelve weeks following the completion of the x-ray therapy, the dogs were operated upon and each of the procedures performed in Groups A to D were repeated once again. In Table V, the results in this group are recorded.

Two fistulas were produced. Both fistulas were associated with hydroureter, hydronephrosis, and infection. In addition, a possible third fistula was developing in an animal which succumbed to peritonitis on the fourth postoperative day. In Fig. 7, the microscopic section discloses the fistulous site in the ureter of animal A-1. The associated infection cannot be seen in the microscopic field portrayed.

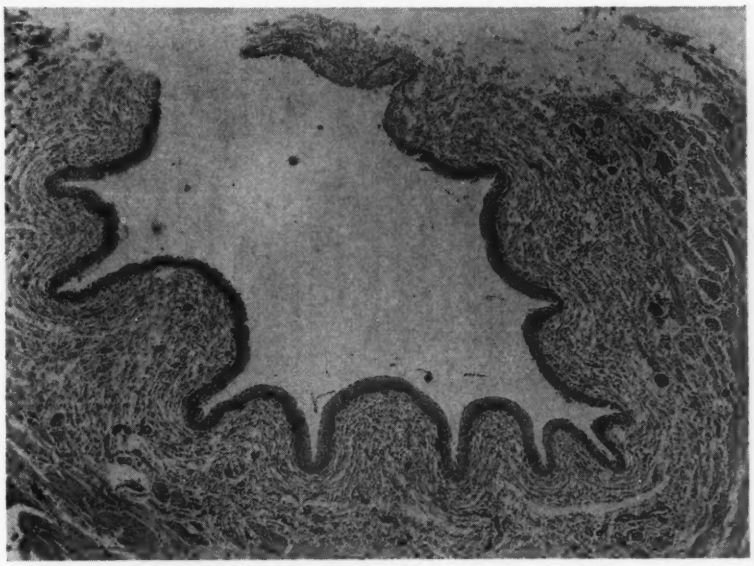

Fig. 7.—Microscopic section of fistula site in the left ureter of Animal A-1 in X-ray Group.

TABLE V. GROUP X-RAY. EACH ANIMAL RECEIVED A COMPLETE COURSE OF DEEP X-RAY THERAPY EIGHT TO TWELVE WEEKS PRIOR TO OPERATION. STUDIES OF GROUPS A TO D REPEATED AS INDICATED

NO.	AMOUNT OF RADIATION	RIGHT SIDE			LEFT SIDE			
		DILATATION	INFECTION	FISTULA	DILATATION	INFECTION	FISTULA	
A-1	3,267 r	0	0	0	+	+	+	
B-2	3,815 r	0	0	0	0	0	0	
C-3	3,815 r	+	+	+	0	0	0	
D-4	3,288 r	+	+	0	+	+	?	(Died fourth postoperative day)

In analysis of the five series of dogs, 75 per cent of all of the animals had either unilateral or bilateral hydroureter and hydronephrosis at the time of autopsy. In the animals that died before the tenth day, the incidence of hydroureter and hydronephrosis was 100 per cent. In an attempt to evaluate this phenomenon, a group of dogs were studied with preoperative and postoperative intravenous pyelograms. The animals were operated upon and the ureters bilaterally isolated, blood supply divided, and hypogastric arteries ligated. The ureters were then traumatized prior to closure of the abdomen.

Fig. 8.

Fig. 9.

Fig. 10.

Fig. 8.—Postoperative intravenous pyelogram reveals bilateral hydroureter and hydronephrosis.
Fig. 9.—Normal preoperative intravenous pyelogram.
Fig. 10.—Postoperative intravenous pyelogram in same animal shown in Fig. 9. Reveals bilateral hydroureter and hydronephrosis.

Twenty-four hours later, the intravenous pyelogram was repeated. At this time, as seen in Fig. 8, there were bilateral hydroureter and hydronephrosis. This subsequently resolved. In preoperative pyelograms of another dog, as seen in Fig. 9, these were entirely normal. In this animal the ureters were isolated, the blood supply divided, and the hypogastric arteries ligated. Before the abdomen was closed, the right ureter was enveloped in polyethylene tubing. Twenty-four hours postoperatively, the intravenous pyelogram was repeated. Again, as seen in Fig. 10, there were bilateral hydroureter and hydronephrosis. Therefore, it appears that the complete isolation of the ureters and ligation of their blood supply will be associated with atony of the ureters. Such a condition would be conducive to the establishment of infection.

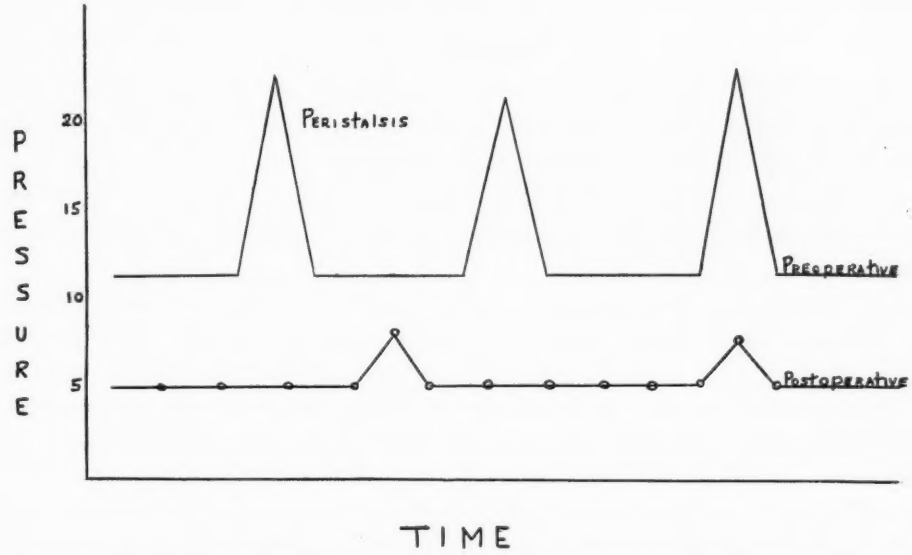

Fig. 11.—Diagrammatic representation of the preoperative and postoperative intraureteral pressures in the human. Pressures are recorded in millimeters of mercury.

Comment

Although it is not feasible to obtain adequate pyelographic studies during the immediate postoperative period in women who have undergone radical hysterectomy and pelvic lymph node dissection, the phenomenon of atony was suspected from the studies in the dog. Some time ago, the opportunity presented itself to study the status of the human ureters twenty-four hours post-radical hysterectomy in a patient who was having profuse bleeding. At abdominal exploration, the ureters and renal pelves were found to be markedly dilated even though there was no obstruction present. Since that time studies have been undertaken in humans to evaluate the status of the ureter during and following radical pelvic surgery. The preliminary findings indicate that there is a marked fall in the intraureteric pressure following isolation of the ureters. As seen in the diagrammatic portrayal of the kymograph records in Fig. 11, there are not only atony, but also a diminution in the strength, frequency, and duration of peristalsis. It is appreciated that this change in peristaltic activity is related in part to alterations in the urine volume

output as demonstrated by Lapides.[4] However, the persistence of low intraureteral pressures following the return of normal urine volume output suggests alterations in the ureteral physiology. This disturbance is corrected after varying periods of time. It has been postulated by Lapides that the tonus and peristalsis of the human ureter are "independent of the central nervous system including the autonomic nervous system and all its ganglia." If further studies corroborate this phenomenon of postoperative atony, the hydroureter and hydronephrosis, seen so frequently on the initial pyelographic studies of post-radical hysterectomy patients, may be on a physiological rather than an obstructive basis as was formerly entertained.

Summary

1. Five series of dogs have been investigated in an attempt to evaluate the factors of blood supply, trauma, infection, radiation, and combinations of these in the production of ureterovaginal fistula.

2. No fistulas were produced as a result of trauma, removal of blood supply, or the isolation of the ureter to prevent development of periureteral adhesions.

3. One fistula was produced in a ureter inoculated with *Aerobacter aerogenes.* Two additional fistulas occurred in dogs whose surgery was preceded by a full course of deep x-ray therapy. The over-all incidence was 12 per cent.

4. In the entire series, the incidence of either unilateral or bilateral hydroureter and hydronephrosis was 75 per cent. This was demonstrated by postmortem and pyelographic studies.

5. Preliminary studies in the human indicate a transient loss of tone and peristaltic activity of the ureters following radical isolation of the ureters in the surgical treatment of pelvic malignancies.

I wish to acknowledge the assistance of Drs. A. Sidney Goss and Richard Link in the animal studies presented in this paper.

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Discussion

DR. ARTHUR M. DAVIDS.—The difficulty in evaluating Dr. Masterson's results lies in the fact that the human ureter is not exactly comparable to that of the dog. Anyone who has worked experimentally with the dog ureter is familiar with its narrow, firm, cordlike structure. The human ureter is a larger structure with a soft distensible muscular wall. In our experimental work of reconstructing ureters and bladders from small bowel segments we routinely transplanted the dog ureters into a segment of ileum. The ureters were firm and narrow and had to be handled a good deal in preparing a fish mouth of the lumen for

implantation. The dog's ureter seems to withstand the trauma well and we had no ill effects such as ureteral fistula or stricture in any of our dogs. Did you produce periureteral hematomas by traumatizing the dog ureter?

DR. MASTERSON.—On occasion we did. The thing most noted was that the ureters became a pinkish-blue or bluish-black color, particularly in their distal 2 to 3 cm.

DR. DAVIDS.—I am sure that the surgeons who perform radical pelvic surgery find that the ureters are easily traumatized. As the ureter is dissected free it must be handled gently or the trauma to the rich vascular bed running along its walls will produce large bleblike hematomas. The musculature of the human ureter is vulnerable and fistulas and strictures are easily produced. This is certainly true even when radical dissections are not performed. Injuries to the ureter may occur when the surgeon inadvertently clamps across the ureter or ties a suture around the ureter. Recognition of this accident with quick removal of the clamp or suture does not always prevent the formation of a fistula or stricture of the ureter. A fistula can occur at the site of muscular trauma without injury to the main lateral vascular supply to the ureter. No fistulas occurred in your series of dogs despite deliberate trauma by clamping. In the human following radical pelvic surgery a fistula may easily occur due to direct injury to a portion of the musculature with resultant necrosis and sloughing. Other fistulas may occur not primarily as a result of direct injury to the musculature but as a result of interference with the vascular supply of the ureter. In such instances strictures, infection, hydronephrosis, and fistulas may occur secondary to ischemia of the ureter. Infection may play an important role as you found in your animals but direct trauma to the human ureter will produce serious sequelae such as strictures and fistulas without gross infection at the site of trauma.

DR. SAUL B. GUSBERG.—I would like only to make the comment that Dr. Masterson suggests that loss of blood supply does not play a part in this injury, and yet I don't know of any other trauma that could occur with radiation plus surgery than a defect in blood supply. I think this is a little bit of evidence that this does play some role.

DR. MASTERSON.—I agree with Dr. Gusberg, it does play a role. It is a question of significance. When we add radiation, we are adding an additional factor which I think largely works through the elimination of the collateral circulation, which may be enough to carry over the ureter in a nonradiated patient.

If I could make a departure from the prepared text, earlier this afternoon I had an opportunity to go over in some detail a very well-prepared and interesting exhibit out in Chicago on a series of radical hysterectomies and in their procedure they do not isolate the ureter from the peritoneum. They leave it in continuity. They preserve the intermediate branch going to the ureter from the iliac or hypogastric arteries and they completely reperitonize the ureter on both sides as well as the pelvis. Dr. Kistner said this afternoon that in their series now, which is close to 80, their incidence of fistula is 8 per cent, exactly in the same range that we are achieving where no consideration has been given to those factors.

DR. GUSBERG.—May I make another comment on your comment with respect to the reperitonization and failure of stripping of the Boston group? This refers, does it not, to the upper four-fifths of the ureter but not to the lower 4 or 5 cm., which is the area in question with respect to blood supply and fistula? It is not possible to do a proper radical hysterectomy without stripping the ureter in this area so that I do not think anybody who pretends to do a radical hysterectomy can do this operation without stripping the ureter in this area. I think the blood supply is injured to the same degree whether or not reperitonization is effected in this area. I might add that the operation as it is carried out in our institution is more or less as you describe it for the Boston group and our incidence of fistula is about the same.

DR. EQUINN MUNNELL.—Our ureteral complications occur a little later than yours. I am sorry you killed your dogs so early because it would be interesting to know what would

have happened if you had let them live 4 or 5 weeks to see what ureteral complications would have developed in that time as well as in 10 to 12 days. I think the majority of our ureteral fistulas have occurred within about 3 to 4 weeks rather than earlier. We have also seen delayed ureteral problems of stricture. We have been more impressed by the importance of ischemia in producing fistulas rather than of infection.

DR. MASTERSON (Closing).—I would comment on what Dr. Gusberg has said. I think that our present feeling regarding this is that the surgical approach to the treatment of uterine malignancy should be as radical and as extensive as it can be within the realm of safety and the well-being of the patient. If a very extensive procedure is not associated with a higher incidence of fistulas, it may very well behoove us if we are going to continue surgery to do the more radical procedure with full knowledge, however, that it is going to be associated with an incidence of fistulas of anywhere from 7 to 12 per cent.

TRANSITIONAL MYOGENIC TUMORS AND SARCOMA OF THE BROAD LIGAMENT

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THE most common mesenchymal tumor of the broad ligament is the leiomyoma, over 400 cases having been published. The sarcoma of the broad ligament, on the other hand, appears to be a rare condition. In 1908, Wack[25] described one case and collected 8 from the literature. Within the next 34 years the literature was replete with reports of sarcoma of the broad ligament. In 1942, however, Pardini[17] published a report of one case of sarcoma of the broad ligament and, after a critical review of all the cases previously published, stated that, according to his view, only 21 of these were real sarcomas. In 1945, Nobili[15] tabulated 24 histologically authenticated cases of sarcoma, and another report by Karoliny and Arvay[8] appeared in 1949. This brings the total of hitherto known published cases of sarcoma of the broad ligament to 25. A plausible explanation of the discrepancy between the numbers of cases recognized by the different authors as sarcomas of the broad ligament will be offered later on in this article.

The older authors[10, 23] have denied the existence of primary mesenchymal tumors of the broad ligament. They thought that these tumors originated from the uterus as pedunculated forms and it was the atrophy of the pedicle which gave the appearance of a homeoplastic growth of the broad ligament. Max Sänger[22] was the first one to point out that all the elements necessary for the formation of such tumors are present in the broad ligament and that myomas, as well as sarcomas, might therefore originate in the broad ligament.

The older concepts of origin now appear farfetched. Most of the reported sarcomas of the broad ligament were rather large. Of those recorded, only 3 were less than 500 grams[11, 15] and the others varied from 920 to 11,300 grams. If such large tumors originated as primary tumors of the uterus, one would expect to find a large pedicle rather than an atrophied one. It is not probable that a tumor should divest itself of a well-formed pedicle.

Histologically, sarcomas of the broad ligament may arise from any of the mesenchymal elements, such as muscle or connective tissue, reticuloendothelial or vascular systems. They may occur as sarcomatous degeneration of a primary myoma of the broad ligament. They may also originate from the nerve tissue. All degrees of maturity ranging from myo-, fibro-, and chondrosarcoma to spindle- and round-cell sarcoma are reported. Giant cells have been frequently described and hemorrhages with pseudocystic areas of necrosis and liquefaction are common.

The ages of the patients reported to have had sarcoma of the broad ligament range from 19[17] to 72,[9] the most common age at diagnosis having been between 30 and 50 years.

The percentage of cases in which recurrence or metastasis has occurred has been difficult to judge because the primary surgical mortality and that due to postoperative complications has been so high (28 per cent). One interesting fact is obvious, however, even in the small series collected from the case reports. In only one case,[13] that is, 4 per cent, has there been a local recurrence, whereas 40 per cent of the cases metastasized. In the remainder of the cases the length of survival is stated to have been for an undetermined period of time even though, in some, very large tumors were removed. Such weights have been recorded as: 1,000 grams,[11] 1,500 grams,[18] 2,000 grams,[15] 5,670 grams,[17] 9,800 grams.[6] Two were the size of a baby's head.[7, 21] In six of these cases of survival beyond the postoperative period, however, no follow-up was available so that their ultimate fate remains unknown. Another patient was seen one and a half years after operation.[15]

Among the smooth-muscle tumors of the broad ligament, there are some which, although they do not show positive clinical features of malignancy, such as invasion or metastasis, cannot be considered entirely benign because of their rapid growth and histologic anaplasia. Two cases of this type are to be described.

The classification of such tumors presents a problem. Similar tumors of the uterus have been named leiomyosarcoma, Grade I, by Wheelock and Warren[26] or low-grade leiomyosarcoma by Davis, Howe, and French.[4]

The questions whether or not terms such as low-grade sarcoma or Grade I sarcoma, respectively, are justified and whether leiomysarcoma can be accurately diagnosed from histologic criteria arise in relation to such cases. The final decision in this controversy properly belongs to the pathologist. In the 2 cases to be presented the intent is merely to draw attention to the occurrence of these tumors of borderline pathology.

CASE 1.—Miss M. K., a 39-year-old, single white woman, had anterior poliomyelitis at the age of 2, with no residual effects. The menses were regular, every 30 days, lasting 4 days. An increasing enlargement of the abdomen noted during the previous twelve months was the only symptom except for a diminished menstrual flow for the previous two years. An Aschheim-Zondek test by another doctor had proved negative.

Physical examination showed a tall, slender white woman in good condition. On abdominal palpation an oval mass, the size of a nine months' gestation was felt, the upper pole being under the costal margin. The introitus was virginal. On rectal examination, the uterus was felt to be enlarged, hard, of irregular contour, and dextroverted. The left side of the pelvis was filled by a round mass which was continuous with the abdominal tumor.

The patient was operated upon on April 15, 1953, with the diagnosis of left ovarian cyst. A low median laparotomy was performed under general anesthesia. A considerable amount of yellow ascitic fluid was present. The uterus was enlarged to the size of a two months' gestation by multiple fibroids. A tremendous tumor filled the whole abdomen, including the epigastrium. The incision was prolonged to 2 inches above the umbilicus and the tumor was brought out from the abdominal cavity.

The tumor was completely covered by smooth and glistening peritoneum. The left ovary was on top of it but completely separate. The right adnexa were normal. The long pedicle of the tumor was investigated and found to be fanning out over the left infundibulopelvic ligament.

The peritoneum over this ligament was split and the left ureter was visualized. The left ovarian artery was dissected, ligated, and cut. Thereafter the whole pedicle was clamped and cut, and the tumor was removed. A typical panhysterectomy was performed. The whole pelvic area was peritonized and all stumps were covered with vesicoperitoneum.

The patient made an uneventful recovery and was discharged on the eleventh day. She has remained under observation and was found to be quite normal on April 10, 1956.

Fig. 1.

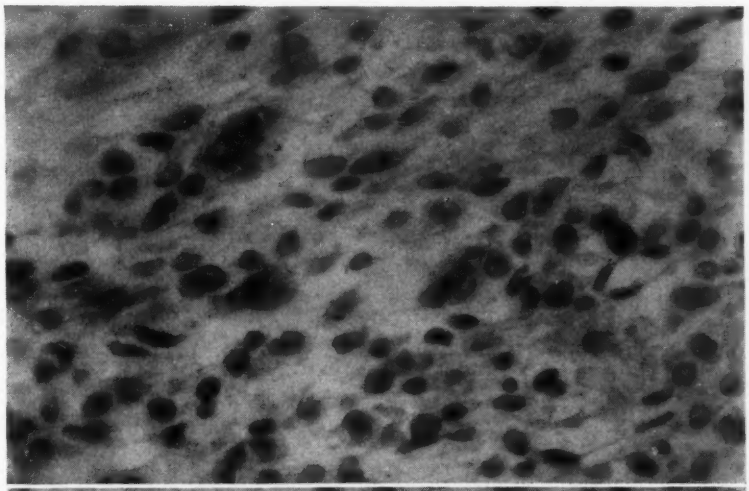

Fig. 2.

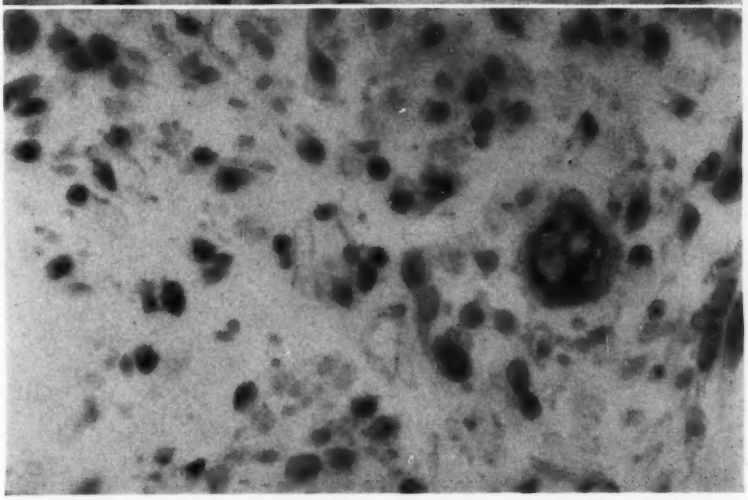

Fig. 1.—Case 1, M. K. Short, ovoid, hyperchromatic nuclei of different size and shape. (×620; reduced ⅕.)

Fig. 2.—Case 1, M. K. Irregularly shaped giant cell. (×620; reduced ⅕.)

Pathological Report.—The uterus with cervix measured 15.0 by 9.0 by 11.0 cm. There were several well-circumscribed, firm, grayish fibroids in its muscular wall, the largest measuring 6 cm. Microscopically, the fibroids of the uterus were composed of interlacing bundles of typical smooth-muscle cells and connective tissue fibers.

The large separate tumor weighed 3,500 grams and measured 35 by 25 by 15 cm. Its substance was soft, grayish, and showed numerous small cystic spaces and dark-red hemorrhages. One of the ovaries was attached to the pole of the tumor by a short, narrow pedicle. Microscopically, the tumor was composed of bundles and sheets of short, plump muscle cells, without any pronounced fascicular pattern. The nuclei of the tumor cells were short, ovoid, hyperchromatic, and showed marked variation in size and shape (Fig. 1). There were scattered mitoses and irregularly shaped giant cells in many places (Fig. 2). Some parts of the tumor were rather vascular and showed marked edema and extensive hemorrhages. The cystic spaces of the tumor were necrotic with edematous pseudocysts.

Fig. 3.

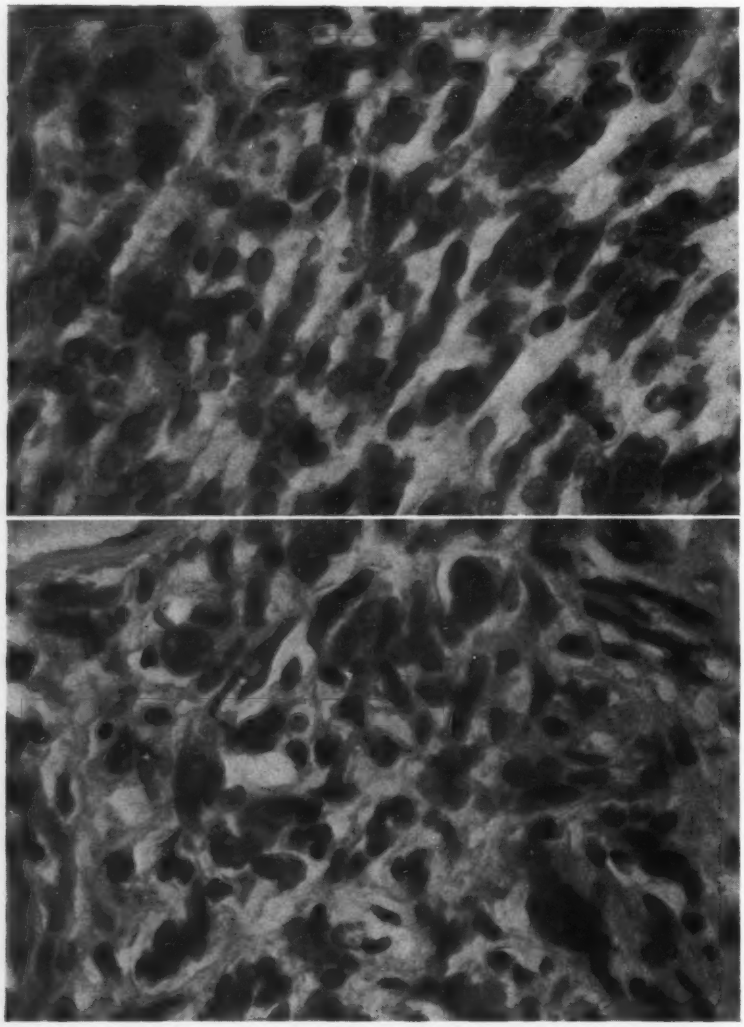

Fig. 4.

Fig. 3.—Case 2, E. P. Great cellularity, hyperchromatism, scattered mitoses. (×570; reduced ⅕.)

Fig. 4.—Case 2, E. P. Polynuclear giant cells in area of degeneration. (×600; reduced ⅕.)

The pathologic diagnosis was: (1) fibromyomas of the uterus; (2) myogenic tumor of the broad ligament.

CASE 2.—Miss E. P., an unmarried white woman of 39 years, presented herself for examination on Nov. 7, 1950, with a history of a recent increase in the amount of her menstrual flow. The past history was largely negative. Menstrual periods had occurred at 28 day intervals, lasting for 4 days, average in amount.

Gynecological examination showed the fundus of the uterus to be apparently normal in size and displaced to the right. To the left of the uterus in the general position of the ovary was a solid 10 cm. mass. The preoperative diagnosis was ovarian fibroma or fibroid of the uterus.

On Dec. 5, 1950, the patient was operated on at the Presbyterian Hospital by Dr. Howard Taylor, through a suprapubic midline incision. The uterine fundus was normal except for a minute subserous fibroid on the anterior surface. The tubes and ovaries were normal.

The previously described mass proved to be retroperitoneal in position in the left side of the pelvis. The left ureter was found medial to the mass. The peritoneum over the mass was incised in a longitudinal manner. By sharp and blunt dissection a round, 8 cm. mass with two smaller masses, 3 and 4 cm. in diameter, respectively, were delivered through this peritoneal incision. A frozen section was done but led to no very definite diagnosis. The abdomen was closed in layers with fine silk sutures. The patient made an uneventful convalescence.

After the final microscopic examination of the pathologic material, it was considered that a recurrence was a possibility, but still so unlikely that no further operation or radiation therapy seemed indicated.

Multiple sections from the various tumors showed an unusual fibromuscular tissue with areas of great cellularity, and some diffuse hyaline degeneration. Some nuclei were hyperchromatic and of different size and shape (Fig. 3). There were large polynuclear giant cells (Fig. 4).

The patient has remained under observation and was reported to be quite normal at a final follow-up examination five and one-half years after operation.

Comment

In transition from the rather common leiomyoma of the broad ligament to the rare leiomyosarcoma, there are some tumors which occupy a borderline position between benign and malignant. They show a varying degree of anaplasia, hyperchromatosis, mitosis, and polynuclear giant cells in areas which are degenerating. Some of them grow rapidly and to a very large size. Their definite classification as either benign or malignant is difficult and may sometimes be determined only by the ultimate fate of the patient. The 2 cases of such transitional myogenic tumors of the broad ligament which are detailed in this article show no tendency to metastasize three and five and one-half years, respectively, after operation.

Certain of the physical characteristics of these tumors are influenced by the anatomy of the broad ligament. The upper part of the broad ligament, the *ala vespertilionis* of the old anatomists, is freely movable, thin, and of loose texture. The lower portion is well anchored, the two leaves of the peritoneal covering being farther apart, and its texture is increasingly dense and vascular. The tumors of the upper part are mobile, pedunculated, more or less encapsulated and easier to remove. The tumors of the lower portion are fixed, poorly defined, and more difficult to excise.

The upper portion of the broad ligament is only rarely the site of mesenchymal tumors because of its paucity of muscle and connective tissue

fibers. If such tumors are present there, however, they may have a slightly better prognosis than the tumors of the lower portion. The large tumor described in the first case report (Miss M. K.) was so located in the upper portion of the broad ligament and this feature may contribute to a further good prognosis in this case.

Summary and Conclusions

The sarcoma of the broad ligament is an unusual tumor. The literature which records 25 proved cases is reviewed critically.

In addition to the mesenchymal tumors of the broad ligament which are of a high degree of malignancy, there are some which are borderline in pathology and upon which a definite diagnosis of malignancy is difficult to make.

Two such cases of transitional myogenic tumors of the broad ligament are presented and offer common significant findings, such as great cellularity, numerous cellular and nuclear irregularities, and polynuclear giant cells in areas of degeneration. These 2 patients are well and apparently free of metastasis or local recurrences after three and five and one-half years, respectively, after operation.

Such cellular tumors of the broad ligament are readily mistaken for sarcoma but actually are not malignant. Their erroneous classification as sarcomatous explains the conflicting reports in the literature about the number of observed sarcomas of this area as well as the claims of cure of malignant neoplasms after removal of very large cellular tumors of the broad ligament.

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A STUDY OF PORPHYRINS IN RELATION TO CANCER

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THE Wood light or filtered ultraviolet light is commonly employed by the dermatologist for the detection of tinea capitis or ringworm of the scalp. It consists of a mercury vapor ultraviolet light filtered through a dark violet glass containing nickel oxide and its rays are in the zone of 3,300 to 3,600 angstrom units. Under this light in a dark room the involved hairs and stumps containing the Microsporon present a fluorescent brilliant greenish glow. When tissues or substances containing hematoporphyrin are illuminated with the Wood light in a semi-darkened environment, they present a flaming red color.

Utilizing this latter phenomenon, Hauser[1] in 1929 described the presence of red fluorescent deposits about the female genitals. He attributed the red fluorescence to porphyrin produced by the decomposition of blood by specific bacterial flora. Kammerer[2] had previously demonstrated that bacteria in the stool can produce porphyrin from blood pigment (hematin).

In 1946 Jones, Shaw, and Figge[3] again described the red fluorescent deposits on the vagina and cervix, but as a possible aid in the detection of malignancy. In several articles previously and subsequently published by Figge and others[4-7] the statement was made that "it has been demonstrated that porphyrins have a tendency to accumulate in neoplastic, embryonic, and traumatized tissues."

Francesco Ronchese[8] also made the following statements relative to cancer: "Advanced epidermoid cancer not evident in the first biopsy may be detected by a Wood light." Although in the same paragraph he stated, "The flaming color is not seen with early carcinoma but only in highly malignant, ulcerated, and necrotic tumors."

Jones, Shaw, and Figge[3] also studied vaginal tampons inserted by 172 volunteer women in a tuberculosis sanitarium near the end of the menstrual period and again about one week after the cessation of the period. A quantity of porphyrins sufficient to saturate the surface and produce intense red fluorescence of vaginal tampons under the Wood light was present postmenstrually in approximately 10 per cent of the women studied and lesser amounts, but still sufficient to cause intense fluorescence, were found in about 40 per cent of the women. The tampons of about 60 per cent of the women studied did not exhibit more than slight amounts of red fluorescent material or none at all. Intermenstrually, traces of faint fluorescence were noted in 10 per cent of the cases. These authors concluded that intense fluorescence intermenstrually should be considered an evidence of abnormal uterine flow probably associated with imperceptible bleeding, which demanded further study

such as curettage and biopsy of the cervix and hence as much attention as visible metrorrhagia. Biopsy of the cervix, however, in a representative group of their cases showing red fluorescence and a control group of others not showing fluorescence failed to demonstrate any evidence of microscopic changes produced by this material. They also emphasized that early visible carcinomas of the cervix may *not* show porphyrin deposits. Therefore, the presence or absence of porphyrin cannot in itself be used as a test to rule out cancer, but should be used to supplement the procedures now recognized, i.e., examination, biopsy, and curettage.

In view of the conflicting statements cited above, the study reported herewith was made to try to evaluate the Wood light fluorescence test and to attempt to determine its practical clinical value, if any.

Method and Results

A. Fifteen placentas were illuminated with the Wood light immediately after delivery. One was a retained placenta. All were negative for porphyrins. The uterine cavity and placenta were illuminated during a cesarean section with negative results on one occasion.

B. Four uteri opened immediately after hysterectomy (2 for fibroids and 2 for unexplained menorrhagia) were negative for porphyrins.

C. Vulvar pads of 26 postpartum patients were illuminated. Eighteen were positive for porphyrins within 48 hours and a few more became positive on the third and fourth days. One patient with threatened abortion, who was curetted because of incomplete evacuation of uterine contents, had positive pads.

D. Single cases of carcinoma of the breast, rectum, sigmoid, colon, vulva, cervix, corpus uteri, and nose were illuminated and found negative.

E. A series of 60 cases were studied by first performing a careful bimanual, including rectovaginal, examination. The cervix was then illuminated with a Wood light through a vaginal speculum. The cervix was then painted with a solution of hematoporphyrin, 100 mg. to 100 c.c., making a solution of 1:1,000. The Wood light was again focused on the cervix. Smears were then taken for fern pattern and for microscopic cytological examination, with the use of the Riley[9] technique of silver staining after the smears were fixed in 20 per cent formalin. The cervix was then inspected with a colposcope and again after the application of 3 per cent acetic acid and a third time after the application of Lugol's solution (Schiller test).

Patients were subsequently supplied with Draghi Detection Tampons.* These tampons were inserted on the day prior to the patient's appearance in the office. They were removed in the office and illuminated with the Wood light and smears taken from them for silver stains.

Four patients in this group of 60 showed the presence of porphyrin in the vulva on illumination. None of these patients had cancer. On illumination of the cervix, 5 patients were found to have some spots which showed red fluorescence under the Wood light: one in a case of previous carcinoma of the breast, one in a case of porphyria, which has been followed for 12 years, one in a Negro patient with pelvic inflammatory disease, one in a patient with a previous thoracoplasty, who had miscarried three times, and one in a case of uveoparotid fever (sarcoidosis) with chronic cervicitis. The tampons were positive in two cases. Unfortunately, tampons were not available for the early cases.

*Furnished by Tampax Incorporated.

Two cases of carcinoma of the cervix were negative to the
The tampons were also negative. My own case was detected by the
and Schiller test, and smears. It was verified by biopsy. Repeat
and illuminations have all been negative. The smears directly from
appeared to afford as good a selection of cells as the smears from the tampons.

F. Recently, an applicator dipped in the hematoporphyrin solution was used to make the vaginal smears. The smear was then examined under the microscope with illumination through the substage with the Wood light. Smears from my case of carcinoma of the cervix cited above examined in this manner disclosed the presence of cells which were golden in color. However, cells from the tampons were also golden in color as were cells from some of the patients who had no malignancy.

Summary

The use of the porphyrin and Wood light test applied grossly to malignancies and to the cervix before and after painting it with hematoporphyrin 1:1,000 is not specific enough to be used as a clinical test.

The tampon cytological technique in combination with a careful gynecological history affords a satisfactory method of mass screening of women for carcinoma of the uterus, because it can be performed without the immediate presence of a physician. However, it cannot supplant the proved methods of periodic investigation which include a careful history, bimanual, specular, and colposcopic examinations, cervical and uterine aspiration smears for cytological examination, and the Schiller test.

Curettage and adequate biopsy are mandatory in any case where these procedures have not proved decisive or have led to suspicion of the presence of malignancy.

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LIMB EDEMA OF PELVIC ETIOLOGY IN WOMEN

Its Evaluation by Means of Pelvic Venography and a Lymphatic Function Test

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THE edema of the arm that follows radical mastectomy for carcinoma of the female mammary gland is one of the most serious shortcomings of the procedure. The importance and frequency of this complication are demonstrated by the number of investigations that have been published about its causes, prevention, and treatment. Conversely, it might be assumed that the edema of the lower limbs, resulting from carcinoma of the uterus or its surgical treatment, is a rather rare occurrence, for very little can be found in the literature about it.[1, 2, 3]

A certain similarity between the edema of the extremity as it occurs with cancer of the breast and in cancer of the uterus may be seen, however. Lymphatic deficiency resulting from the trauma to the major vessels of the limb from excision, fibrosis from external irradiation, and infection has each been held partly responsible following operation for each disease.

It is generally recognized that the swelling may be caused either by lymphatic blockage or by venous obstruction. The clinical differentiation of these two conditions is rather easy in an acute stage, but it may be difficult when the edema has become chronic. A useful approach to the study of the pathology of peripheral vessels, both venous and lymphatic, has been provided by venography and by a lymphatic absorption test. The former procedure has been successfully applied by Veal[4] in the evaluation of postmastectomy chronic edema and lately by Dalali and associates[5] to the study of the pelvic veins. A lymphatic absorption test has recently been devised by Ju,[6] a member of the staff of this institution.

Both of these methods have been used by us in the evaluation of chronic edema of the lower limb in a series of patients who had recently undergone surgical treatment for carcinoma of the uterus, as well as in a few patients suffering from edema of the legs resulting from pelvic malignancy without surgery.

Venous Edema or "Phlebedema"

Venous edema is characterized by being mostly distal (acromelic), depressible, reducible by recumbency, often painful. It supervenes promptly after surgery. This "phlebedema" is due to occlusion of the main vein of the limb, caused by thrombosis, by tumor that either invades the lumen of the vein or exerts an external pressure on it, or by benign scar tissue.

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In the evaluation of the thrombotic disease of the limbs, venography has proved to be an excellent means of diagnosis in the hands of Hellstein,[7] Bauer,[8] Veal,[4] and Russo and co-workers,[9] who were able to demonstrate venous obstruction in a high percentage of cases. Veal concluded that recurrence is by far the most common cause of such venous obstruction. A small nodule is sufficient to cause complete obstruction of the vein.

The chronic stage of the edema is characterized by fibrous hyperplasia of the skin and subcutaneous cellular tissue. This has been termed "fibroedema" and represents an irreversible condition. According to Bauer[8] the indurative alterations which follow a long-standing thrombotic edema are due to venous stasis with insufficiency of the compensatory system (collateral circulation). Hellstein,[7] Martorell,[2] and Veal[4] believe that fibroedema is the result of lymphatic obliteration secondary to the venous edema.

Lymphatic Edema or Lymphedema

The lymphatic edema of the limb is harder than the venous edema, is less reduced by recumbency, appears late, and develops slowly. It frequently involves the entire limb and even at times the neighboring region (rhizomelic). Usually it is not accompanied by pain.

The lymph stasis occurs primarily as a result of an obstruction of the lymphatic channels which may be produced by inflammatory or noninflammatory processes. As a result of this obstruction intralymphatic pressure increases, causing dilatation of the lymph vessels with subsequent insufficiency of the valves and further stasis of lymph. Since the lymph is an optimum culture medium for the growth of fibroblasts, these proliferate rapidly, producing sclerosis and still further stasis. Inflammation is very apt to occur under these conditions and contributes to a vicious circle that leads to the picture of "elephantiasis chirurgica" described by Halsted[10] as a complication of radical mastectomy.

The defect resulting from the excision of axillary lymph nodes is considered by Devenish and Jessup[11] to be the predominant factor in the production of postmastectomy edema. Obstruction of the lymph vessels by radiation fibrosis was found by Daland[12] and Oberhelman[13] to play an important role in the development of arm swelling following radical removal of the breast.

In Veal's series, only 10 per cent of the cases were believed to be primary lymphedemas and in these venograms failed to reveal venous obstruction. The clinical difficulty of ascertaining the cause of limb edema is emphasized by the observation of Villasor and Lewison,[14] who failed to make out any determining factor in 57 per cent of their cases of postmastectomy edema.

Methods and Techniques

A. Pelvic Venography.—A slight modification of the technique described by Dalali and associates[5] was used to demonstrate the pelvic veins. The patient is first placed on the x-ray table and a rubber compression bag is applied a little above the umbilical region. When the femoral vein can be easily located, it is punctured by means of an 18 gauge needle. The needle is

then connected with a 50 c.c. syringe through a plastic venotube. Whenever obesity or a marked edema makes location of the femoral vein difficult, the posterior retromalleolar vein is exposed by a small incision and a plastic venous catheter introduced into it and connected with the needle.

One flat film is taken prior to the injection of the radiopaque substance in order to be sure of the correct position of the patient. Neo-iopax* in 75 per cent concentration is injected, 50 c.c. or less in each side, at a rate of 1 to 2 c.c. per second. The second film is taken about 10 seconds after the injection is started. Soon thereafter and while the Neo-iopax is still being injected the rubber bag is inflated and the third radiogram taken. When the needle has been inserted in the ankle vein, the second film is exposed 15 to 18 seconds after the injection is begun, and the third film taken as close as possible to the second one. The film size is 14 by 17 inches; the exposure 30 Ma.-seconds, at an average of 85 kv. The target film distance is 40 inches.

As the only complication of the procedure, we encountered a few times a paravenous infiltration of the radiopaque material. In these cases, multiple local infiltrations with Wydase† caused the disappearance of the substance (as checked by x-ray) within 12 to 18 hours. In only two such cases did the infiltration persist longer, one resulting in a local abscess which required incision and drainage.

In regard to interpretation of the venograms, we considered venous function to be impaired, as a result of partial or complete obstruction, only when the x-ray demonstrated a clear-cut collateral circulation, in addition to the nonvisualization or narrowing of the vein. This is essential if one is to avoid misinterpretation of radiograms where an apparent narrowing of the vein is due to technical defect in its filling. When doubt of this kind was present, the test was repeated either at the same sitting or a few days later. Satisfactory films were obtained in 14 of our cases.

B. Lymphatic Function Test.—The lymphatic function test of Ju is based on the known principle that the protein particles are almost entirely removed from the tissue space by the lymphatic system. Under normal conditions in fact only a very small amount of protein leaks out through the blood vessel wall.[15, 16] The amount is greater, however, if the venous pressure is raised or the permeability of the capillary wall increased.

Since the permeability of the blood capillary wall to proteins is low and there is a positive pressure within the lumen, the protein particles in the tissue space are drained almost completely through the lymphatic channels. A delayed absorption of the protein particles from the tissue space indicates an impairment of the lymphatic function. A normal or abnormal lymphatic absorption can be detected by injecting into the tissue space a radioactivated protein, such as I^{131} albumin, and by following its radioactivity at regular intervals.

Ju, experimenting with dogs, concluded that I^{131} albumin was not significantly absorbed in the venous system, but almost exclusively by the lymphatic channels.

In the clinical application of the test, Ju encountered some difficulty due to the inconstant relationship between the radioactivity and the protein concentration as a result of the steady decay of the I^{131}. This problem was solved in the present studies by the dilution of I^{131} albumin with the patient's own serum (to avoid complications due to sensitization of the patient to a foreign protein).

*Neo-iopax, proprietary name for sodium iodomethamate.
†Wydase, proprietary name for a preparation of hyaluronidase.

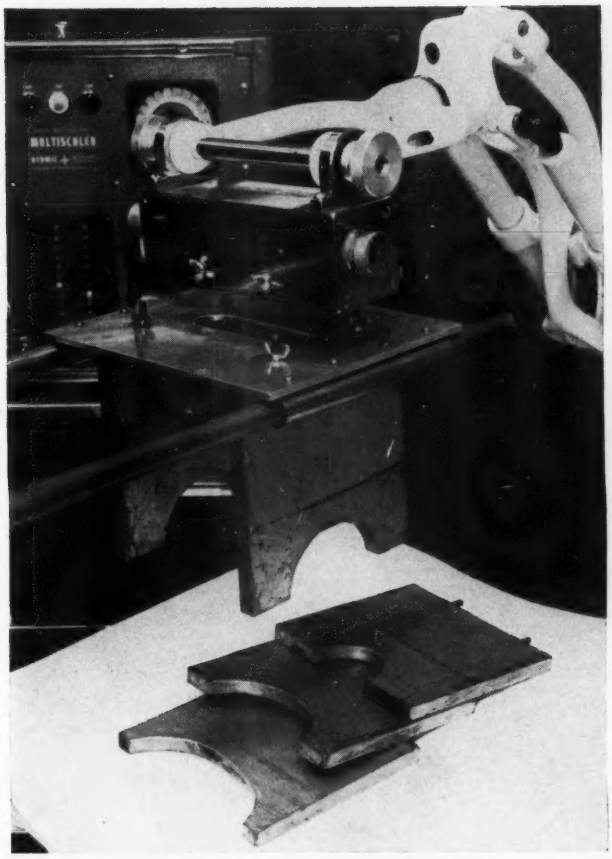


Fig. 1.—Instruments for I^{131} albumin absorption test. From left upper to right lower part of photograph: (1) Scaling unit: Model 1228 Timer Unit, Multiscaler. Atomic Instrument Co., Cambridge, Mass. (2) Bismuth cathode counter. (3) Lead shields and their support.

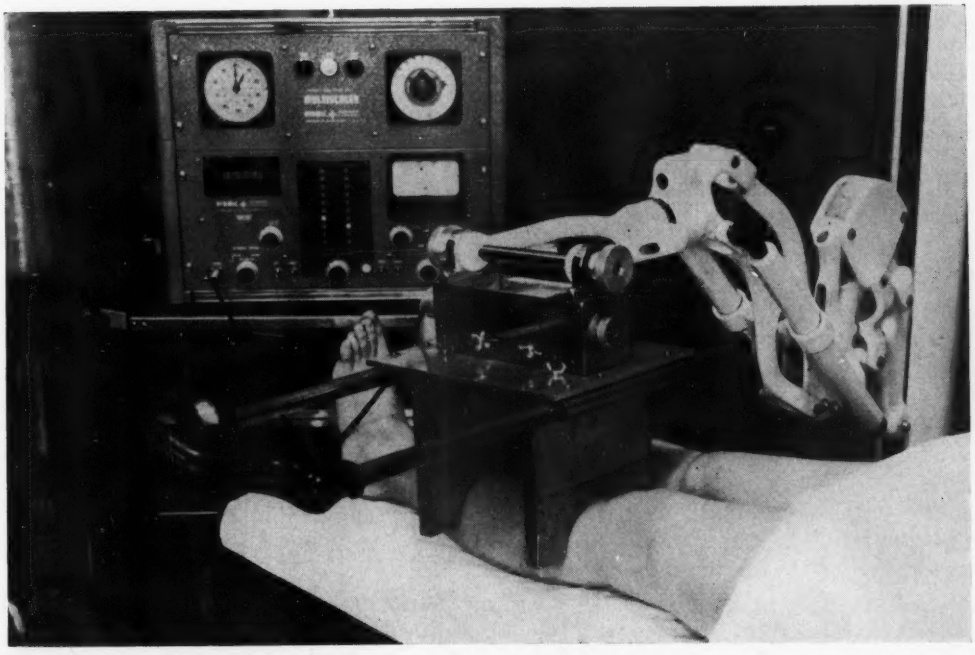


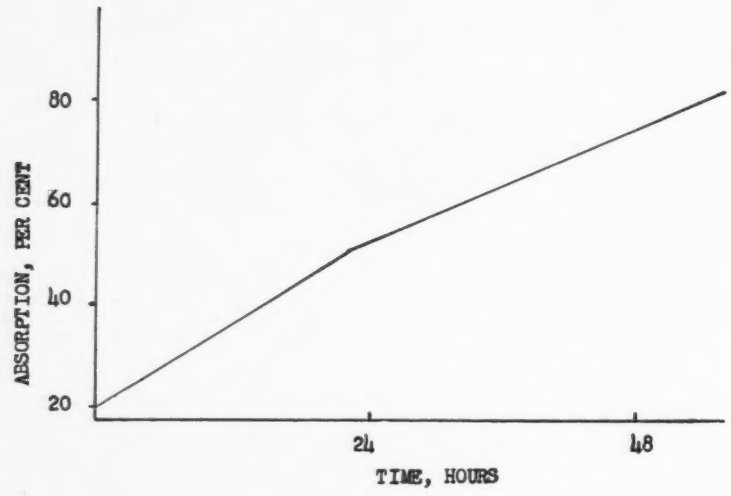
Fig. 2.—Instruments for I^{131} albumin absorption test in use.

In the actual test, 2 c.c. of the patient's own serum, plus 40 microcuries of I^{131} albumin are mixed with 3 c.c. of normal saline solution. By this means, the variation in protein content is small, and the amount of I^{131} is constant. Actually the maximal deviation of the protein content in the testing reagent is not greater than 2 per cent, a degree of error permissible in clinical tests.

Technique of Lymphatic Function Test

The extremity to be tested is placed in a horizontal position and is then divided into longitudinal segments, 6 inches in length, four or five in number according to the length of the limb concerned. The counter, a bismuth cathode tube, having a window with dimensions of 1 inch by 6 inches, is adjusted to the ink markings on the limb which have been made in such a way that the tube covers the whole length of each part to be measured.

Normal I^{131} Albumin Absorption Curve Obtained From the Averages of 10 Control Cases.



AVERAGE ABSORPTION: 24 hours - 55.1 per cent
(44.0 to 69.2 per cent)

48 hours - 77.4 per cent
(72.4 to 87.0 per cent)

Fig. 3.

The testing solution, composed of 3 c.c. of sterile saline solution, 2 c.c. of the patient's own serum, and the amount of I^{131} albumin containing 40 microcuries of I^{131}, is injected in the dorsum of the foot, very close to the ankle. Immediately afterward the radioactivity is measured at the exact positions indicated by the previous ink marks; radioactivity from the adjacent areas of the leg is screened out by lead shields 1 inch in thickness. The bismuth tube is adapted to a special support that is easy to handle and to move in all directions (Figs. 1 and 2).

After 24 and 48 hours, the radioactivity is measured again over each segment. The reduction in radioactivity due to natural decay of I^{131} is calculated and corrected for. The absorption of the testing solution can be computed

in percentages according to the rate of true disappearance of the radioactivity at the site of the injection. The background is of course measured each time, preceding and following all measurements.

According to Ju, the findings for the test are as follows: at least 30 per cent or more absorption after 24 hours and 75 per cent or more after 48 hours. The actual average values were 54.9 per cent (44 to 60 per cent) and 77.1 per cent (64 to 85 per cent) after 24 and 48 hours, respectively.

Our own normal curves of absorption of I^{131} albumin were constructed by performing the test in 10 cases of apparently normal extremities. The patients selected had no evidence of pelvic disease, nor did they have signs of cardiovascular disorder, kidney damage, or dysproteinemia. No surgery had been done on their pelvic organs. We too found that the absorption of the radioactive iodine followed a fairly constant curve. The average absorption of the I^{131} albumin was 55.1 per cent (44 to 69 per cent) and 77.4 per cent (72.4 to 87 per cent) after 24 and 48 hours, respectively (Fig. 3). Since these studies of control cases showed that there is a normal variation in the lymphatic absorption in different individuals, we arbitrarily established as a minimum for the normal a 45 per cent absorption after 24, and 65 per cent after 48 hours, respectively.

As the curves of absorption are almost straight, we shall for simplicity in the outlining of our results consider only the percentage of absorption after 48 hours.

In several cases the measurements were made with the bismuth cathode tube and, soon afterward, with a scintillation counter, an instrument supposed to be more sensitive. The comparison between the two series of data was entirely satisfactory.

Material

Forty-one cases have been studied, 10 of which were controls, as said above, and 29 carcinoma of the uterus. Table and discussion will be based on the latter group only.

TABLE I. PELVIC VENOGRAMS AND I^{131} ALBUMIN ABSORPTION TESTS

	CLINICAL DIAGNOSIS		
	NO EDEMA 10 CASES	PHLEBEDEMA 6 CASES	LYMPHEDEMA 13 CASES
Venogram.—			
Normal	-	3	8
Abnormal	-	1	2
Lymphatic Absorption.—			
Normal	7	3	1
Abnormal	3	3	12
Both Tests.—			
Abnormal	-	0	2

The series of 29 patients may be divided into three groups (Table I): Group A included 10 patients who had no edema of the lower limbs. Group B consisted of 6 patients who had edema of the lower extremities with the clinical characteristics of phlebedema. Group C was composed of patients with edema of the legs that showed clinical evidence of being of lymphatic origin.

Results

Group A.—In the 10 patients of this group there was no edema of the extremities. Pelvic venograms either were not performed or were unsatisfactory.

In 7 the lymphatic absorption test was found to be normal. Four had untreated carcinoma of the cervix; the pelvic examination had made out masses that we regarded as involved lymph nodes of the pelvic wall. In none of these patients, however, did the histological examination of material obtained at subsequent operation confirm the clinical diagnosis. One patient had had a radical hysterectomy and bilateral lymph node dissection, preceded by a cycle of external irradiation to the pelvis, two years before. The last 2 cases of this group with normal lymphatic absorption test had received a full irradiation treatment, i.e., radium and x-ray for carcinoma of the cervix, Stages I and II according to the International system of classification. The radiation therapy had been followed by bilateral extraperitoneal lymph node dissection at three- to six-month intervals. In these 2 patients the lymphatic test was done twice, before and two weeks after the operation, and it was normal in all instances.

Fig. 4.—Normal bilateral pelvic venogram. No compression was exerted on the inferior vena cava. Note the absence of collateral circulation and of retrograde flow into the internal iliac veins.

In 3 patients of Group A the lymphatic absorption test showed impairment. One patient had had a radical hysterectomy performed for an untreated carcinoma of the cervix. She had a normal I^{131} albumin absorption test prior to the operation and again one week thereafter, the figures being 65.0 per cent and 73.2 per cent after 48 hours, respectively. After the operation the patient had a full cycle of external irradiation to the pelvis (5,000 r,

tumor dose, on the 2 million volt machine). One month after the irradiation was finished the lymphatic absorption test was repeated and showed a definite impairment, the absorption being only 53.6 per cent in 48 hours. The other two patients had received full irradiation treatment, i.e., radium and x-ray, for carcinoma of the cervix, followed by extraperitoneal bilateral lymph node dissection, respectively, three and five months thereafter. In both cases the test was negative prior to the operation, but it showed lymphatic function impairment, respectively, five and three months after the operation. It is worth noting that in one of them the test gave a normal reading when repeated only two weeks after the surgical procedure.

Group B.—The 6 patients of this group had edema of the lower limbs with the clinical characteristics of phlebedema.

Satisfactory pelvic venograms were obtained in 4 of them, and in 3 failed to show venous obstruction (Fig. 4). In all 3 the lymphatic absorption of I^{131} was delayed. Two of these patients had had a full cycle of external irradiation

Fig. 5.—Complete obliteration of the two common iliac veins. Collateral circulation through internal iliac, obturator, lumbar, lateral sacral, and circumflex veins. Patient had chronic bilateral phlebedema of the lower limbs. Obliteration of inferior vena cava and both common iliac veins demonstrated at autopsy due to tumor. I^{131} albumin absorption test in this patient was normal.

to the pelvis for carcinoma of the cervix, three and six months, respectively, prior to our tests, and the edema had developed during the treatment itself. Also, the third patient had received irradiation treatment by both intracavitary radium and x-ray one year before, followed by a total pelvic exenteration, performed at the Francis Delafield Hospital shortly prior to our study.

The fourth venogram showed bilateral obstruction of the external iliac veins, and in this case the lymphatic absorption test was normal. In this patient the edema was bilateral and localized at the feet and ankles. The swelling was of a few months' duration, rather soft, painful, and reducible by recumbency. The patient had had a radical hysterectomy followed by external irradiation to the pelvis performed six years previously for carcinoma of the cervix. There had been no clinical evidence of recurrent disease, but several months after the tests she died. At autopsy, cancer was found to be completely occluding the inferior vena cava just above the bifurcation. The pelvis itself was free of disease and no involved pelvic lymph nodes were found. The venogram (Fig. 5) shows complete obliteration of the two common iliac veins just below their conjunction. The lower portion of the inferior vena cava is also not visualized. An intense collateral circulation is well shown, through the internal iliac, the obturator, and lumbar veins, as well as through the lateral sacral and the circumflex veins.

Fig. 6.—Pelvic venogram showing complete nonvisualization of the right external iliac vein. Collateral circulation through the circumflex, obturator and internal iliac veins. Patient developed edema following irradiation and bilateral extraperitoneal lymphadenectomy for carcinoma of the cervix. Edema was on the right side. I^{131} albumin absorption test showed lymphatic impairment.

In the last 2 cases of clinical venous edema no satisfactory venograms could be obtained: in both cases the I^{131} albumin absorption test was normal.

Group C.—The 13 patients of this group had edema of the lower limbs that showed the clinical characteristics of being of lymphatic origin. Four patients had a pelvic recurrence of carcinoma of the cervix, which had been treated by

irradiation one to six years previously. Two had recurrence in the pelvis of carcinoma of the endometrium previously treated by irradiation. Two had had radical hysterectomy and bilateral pelvic lymph node dissection; neither one had received irradiation therapy. One patient had had an anterior pelvic exenteration one month prior to our study; she had received a cycle of external irradiation three years before. The last 4 patients of this group developed edema following irradiation treatment for carcinoma of the cervix and subsequent extraperitoneal bilateral lymph node dissection. In all these cases but one, the lymphatic absorption test did show impairment, whereas, out of the 10 satisfactory venograms that were obtained, 6 showed a normal venous pattern in the pelvis, 2 showed a narrowing and 2 occlusion of the external iliac vein. It seems worth while to report on the details of these latter 4 cases.

They all had received full irradiation treatment, i.e., radium and x-ray for carcinoma of the cervix, Stages I and II according to the League of Nations Classification. The irradiation therapy had been followed at three- to

Fig. 7.—Pelvic venogram shows irregular narrowing of the right external iliac vein, with filling defects. Collateral circulation through the circumflex, obturator, and internal iliac veins. Patient developed right leg edema following radiation therapy and bilateral retroperitoneal lymphadenectomy for carcinoma of the cervix. I^{131} albumin absorption test showed impairment of the lymphatic function.

six-month intervals by extraperitoneal bilateral pelvic lymph node dissection. At the time of our observation, two weeks to eight months after the operation, these 4 patients presented unilateral edema of the lower limb that had developed within one to three weeks after the operation. The clinical characteristics of lymphedema were present in all of them. The edema, rhizomelic,

was very marked, the circumference of thigh and leg measuring 3.5 to 6.0 cm. more than the normal side. The thickening of the skin and subcutaneous tissue was very marked, especially in 3 of them, in whom the term "elephantiasis" could be used. The patients had no subjective complaints. In all of them the thigh appeared to be relatively much more enlarged than the ankle and leg.

One patient, who developed the edema immediately after the operation, had a venogram (Fig. 6) that showed a complete nonvisualization of the right external iliac vein, and a clear-cut collateral circulation through the circumflex, the obturator, and the internal iliac veins. The lymphatic absorption test was definitely delayed, with only 19 per cent absorption in 24 and 39 per cent absorption in 48 hours.

Fig. 8.—Pelvic venogram showing irregular narrowing of the external iliac vein on the right side. No collateral circulation. Patient developed right leg edema following retroperitoneal bilateral pelvic lymph node dissection for an irradiated carcinoma of the cervix, Stage I. I^{131} albumin absorption test showed impaired lymphatic function.

Another patient developed edema of the right leg three weeks after the operation. Eight months later, when we saw her, the leg presented the typical aspect of "elephantiasis chirurgica." The venogram (Fig. 7) shows very well a marked narrowing of the right external iliac vein, irregular with mottling and filling defects, and a diversion of the venous flow through the circumflex, obturator, and internal iliac veins. The I^{131} albumin absorption test showed impairment of the lymphatic function also, with 61 per cent absorption in 48 hours.

The third patient of this subgroup of 4 with edema of lymphatic origin following extraperitoneal pelvic lymph node dissection developed edema of the right lower limb one month after operation. One month later she came to us with a very marked lymphatic edema of the entire extremity. In this patient the venogram (Fig. 8) shows an irregular narrowing of the external iliac vein. A second venogram was taken and the picture looked the same, but in neither instance could any collateral circulation be made out. The I^{131} albumin test, however, showed decreased lymphatic function: 58.7 per cent absorption in 48 hours.

The last patient developed edema of the right leg one month after the operation. One month later, when our tests were performed, the edema was manifestly of lymphatic nature, and rather marked. The venogram showed a picture very much like the one just described for the previous case (Fig. 8). The lymphatic absorption test, however, gave only 39.6 per cent absorption after 48 hours.

Intermediate Summary of Results of Tests

The I^{131} albumin absorption test showed a high absorption rate in the 10 control patients with no edema and no pelvic disease.

In Group A, 10 patients with no edema but either with uterine carcinoma or after operation therefor, 7 showed a normal lymphatic function: 4 had had no irradiation treatment to the pelvis, one had received it two years previously, and two had had a full irradiation treatment and extraperitoneal bilateral lymph node dissection shortly prior to our studies. In these latter the test was performed two weeks after the operation. But, in 2 other patients who had had the same treatment for carcinoma of the cervix the test showed impairment of lymphatic function several months after the operation. In another case of this group the I^{131} albumin absorption test was found to be normal after radical hysterectomy, but delayed following postoperative irradiation therapy to the pelvis.

Group B included 6 cases in which the diagnosis of phlebedema has been formulated on a clinical basis. In 2 of them the lymphatic absorption test was normal. In 3 the pelvic venogram was normal and the I^{131} albumin absorption delayed. All had received irradiation therapy for carcinoma of the cervix. In one patient the venogram showed bilateral obstruction of the external iliac veins; the lymphatic test was then normal.

In 12 of the 13 patients of Group C the clinical diagnosis of lymphedema was confirmed by our studies. The venogram showed venous occlusion in 2. Out of the 13 cases, 11 had received irradiation treatment to the pelvis for carcinoma of the uterus.

General Comments

As we have pointed out, it may be easy to differentiate lymphedema from phlebedema in the acute stage of the disease, but it is not so easy when the edema has become chronic. The usefulness of pelvic venography and of the I^{131} albumin absorption test as clinical diagnostic aids seems to us to have been demonstrated.

The lymphatic function test demonstrated impairment in 12 of the 13 women who showed clinical evidence of lymphedema of the lower limbs. It was normal in the 4 women who had no edema and no lymph node involvement by tumor.

Pelvic venography could unfortunately not be performed or else the results were unsatisfactory in 15 of the total of 29 patients studied. Yet it

gave us very interesting information. It showed a definite venous obstruction in one patient in whom there were no signs of recurrence of the cervical carcinoma that had been operated upon six years before. The patient had bilateral phlebedema of the lower limbs. The I^{131} albumin absorption test gave a normal result. Later on, the autopsy demonstrated invasion by tumor of both common iliac veins.

In 2 women treated by extraperitoneal pelvic lymph node dissection, who had developed postoperative signs of lymphedema, the venograms showed occlusion of the pelvic veins, probably to be regarded as the initial cause of edema, upon which a chronic irreversible lymphedema was later superimposed. The lymphatic function test showed a delayed absorption in both cases.

The investigation carried out gives us a basis for some discussion of the etiology of chronic edema of the legs in gynecological patients.

1. Irradiation of the pelvis alone plays an important role in this respect. Our tests demonstrated an impaired lymphatic function in almost all of the cases previously treated by external radiation, whereas the tests proved normal in patients who had received none. The influence of radiation fibrosis upon development of limb edema was further demonstrated by studying one case in which we obtained normal data on two occasions prior to a cycle of external radiation, but found definitely impaired I^{131} albumin absorption after irradiation.

2. As to the importance of infection as an etiological factor of limb edema, we were not able to demonstrate it. Significantly, we had a few patients with infection and even disruption of their abdominal and inguinal wounds, who did not develop edema of the legs, and in whom the lymphatic function tests were normal.

3. Injuries to the pelvic veins during the lymphadenectomy, and consequent changes of them, seem to have some importance in the production of postoperative edema. This was proved by venography in 2 of our cases (Figs. 6 and 7). It appears that a clinically silent process of thrombophlebitis developed in these cases shortly after the operation, with the production of leg phlebedema, followed by a superimposed chronic lymphedema, due to a lymphatic obliteration itself secondary to the venous edema (Veal, Martorell, and others). In these cases the I^{131} albumin absorption test showed an impairment of the lymphatic function.

4. The excisional defect of the pelvic lymph nodes seems itself to be a significant factor in the production of postoperative edema of the lower extremities. Ten out of 14 patients who had had pelvic lymph node dissection showed impairment of the lymphatic function following operation, whether or not they developed clinical edema of the leg.

It is perhaps useful to consider some contrasts in the results obtained in patients treated on the one hand by extraperitoneal and on the other by intraperitoneal dissection. In a few patients of both types the lymphatic function test after the operation was repeated two and three times. In all of these the lymphatic drainage from the lower limbs was normal, if not increased, shortly

after the operation, as if the lymphatic channels transected by surgery were draining freely into an empty extraperitoneal space. When repeated later on, the tests performed after the two types of operation did not remain the same. Tests on patients who had had a radical hysterectomy with transperitoneal lymph node dissection persisted as normal, whereas tests done after extraperitoneal node dissection eventually showed impaired lymphatic drainage.

At least a hypothesis may be offered for this difference. Perhaps after intraperitoneal dissection the lymph, collected in a sort of extraperitoneal pool, is continuously drained through the previously opened peritoneum, whereas after extraperitoneal lymphadenectomy it is held in such a pool, compressing the cut end of the lymph channels and impairing their draining function.

Some observations were made in an attempt to check this assumption. A Penrose drain was inserted through the abdominal and the inguinal wounds of a few patients. Albumin I^{131} was injected in the ankle as described, and fluid was collected through the drains. The amount of fluid obtained from patients who had been operated upon by radical hysterectomy and lymphadenectomy was scanty and showed a low rate of radioactivity. On the other hand, in 2 patients who had undergone extraperitoneal lymph node excision, we collected a large amount of fluid, on which the counts were significantly high.

From this study we also think that a few prophylactic measures may be suggested to prevent postoperative edema of the lower limbs.

1. Prophylactic anticoagulant therapy may be of use in the form termed phlebedema.

2. Trauma to the pelvic veins must be minimized by meticulous sharp dissection.

3. Dead spaces must be obliterated as far as possible by careful approximation of tissue and perhaps by the use of Gelfoam.

4. Drainages through the inguinal wounds should be established routinely after extraperitoneal lymphadenectomy, in order to avoid collection of lymph in dead spaces with its consequent risk of infection, and eventual excessive scarring.

5. Early ambulation of the patient and graded exercise of the legs should be encouraged.

6. Elevation of the leg and the use of elastic stockings should be recommended as both preventive and curative treatment.

General Summary

The problem of the clinical differentiation between venous and lymphatic edema of the lower limbs of pelvic etiology in women has been emphasized.

Two techniques of evaluation have been usefully applied: pelvic venography and a lymphatic absorption test.

A lymphatic function test, based on the absorption of I^{131} albumin, has been applied in 10 control patients, 15 patients with uterine carcinoma, and 14 patients operated upon for uterine carcinoma by some procedure involving bilateral excision of the pelvic lymph nodes.

Fourteen satisfactory venograms were obtained.

The importance of several factors in the production of leg edema of pelvic etiology in women has been demonstrated. These factors include postoperative changes in the pelvic veins, the creation of dead space, and radiation therapy to the pelvis.

Conclusions

1. Pelvic venography and the I^{131} albumin absorption test have been proved to be useful clinical aids in the differentiation between phlebedema and lymphedema of the lower extremities.

2. External irradiation to the pelvis seems to be a rather important contributing factor in the production of leg lymphedema.

3. Infection could not be proved in our studies to be a frequent contributory factor in this respect.

4. Trauma to the pelvic veins during the process of lymphadenectomy is another rather important element in the production of postoperative leg edema.

5. The creation of an extraperitoneal dead space as a result of lymphadenectomy seems to be more important than the actual excisional defect itself, in the development of postoperative lymphedema of the lower extremities.

We would like to thank Dr. A. Lough and Miss M. Melton of the Isotopes Laboratories, and Dr. A. Bachman and Dr. D. Bate of the X-ray Department at the Francis Delafield Hospital of the City of New York for their cooperation and very helpful suggestions.

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THE ELECTROLYTES OF THE HUMAN UTERUS AND THEIR POSSIBLE RELATION TO FUNCTIONAL ACTIVITY*

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ANALYSES of the electrolyte content of human uteri have been reported only by Winkler[1] and Kruger.[2] Such data are of importance for several reasons. First, the uterus is an organ from which smooth muscle can be readily isolated in large amounts free of nonmuscular tissues (endometrium, epithelium) which ordinarily plague attempts to analyze smooth muscle. Thus the electrolytes of parts of the human uterus may approach more nearly those of "pure" smooth muscle. Second, the uterus has an organized activity which is influenced by hormonal, mechanical, and other factors. The basis for this organization is unknown, but it is conceivable that the pattern of elecrolyte distribution might explain differential excitability and spontaneous activity. Finally, uterine activity may become disorganized. At present there are no satisfactory explanations of the mechanism of disorganization, and therefore there is no accepted rational therapy. If an abnormality of electrolyte pattern could be correlated with changes in uterine activity, it would provide evidence of a causal relation between uterine electrolytes and activity. Conceivably, this might lead to a more satisfactory treatment of abnormal uterine function.

Methods

Human myometrium removed at hysterectomy under spinal anesthesia has been taken for electrolyte analysis. In order to investigate the possibility of a spatial pattern of electrolytes, the myometrium was separated into fundus, midsegment, lower uterine segment, and/or cervix. In some cases, endometrium of the corpus has also been examined. Blood samples were taken to obtain an estimate of extracellular electrolyte concentrations.

The tissues were blotted and placed in water-tight Turtox weighing jars. In these jars tissues were found to lose negligible amounts of water over a six-hour period. The jars and contents were weighed as soon as possible (usually within four hours). The tissues were then dried to constant weight at 105° C. and reweighed to determine water content. They were then ground and divided into portions for duplicate chloride, sodium, and potassium analyses. Tissue chloride was determined by the method of Van Slyke[3] as modified by Wilson and Ball.[4] For sodium and potassium analyses the tissue was digested with concentrated nitric acid, redissolved in dilute sulfuric acid, diluted to an appropriate volume. Plasma and tissue cations were determined with a Jahnke flame spectrophotometer, using lithium as an internal standard. Plasma chloride was determined by the method of Schales and Schales.[5]

*This work was supported by the National Research Council of Canada.

Extracellular and intracellular sodium and potassium concentrations were calculated by the method of Manery[6] assuming that human plasma contains 930 ml. of water per liter of plasma and that the Donnan distribution ratio is 0.94 for sodium and potassium, and 0.98 for chloride.

Results of Investigation

The Water Content of Uteri.—Analyses of 8 uteri have been carried out. It was found that the uterine water content of various specimens showed considerable variation (Table I). This variation was related to the status of the uterus when removed. In 5 of the uteri in which the water content was relatively high the uteri were not bleeding and in the other 3 in which it was lower the uteri were bleeding when removed. This difference in water content was consistent throughout all portions of the myometrium, but was most pronounced in the cervix. In tissues with high water content the endometrium itself generally had the highest water content, with the cervix next, the fundus next, and the midsegment least. In the tissues from bleeding uteri the endometrium again had the highest water content (even in cases with pathological bleeding), with the fundus next, the midsegment containing less, and the cervix least. The difference in water content between these two groups of uteri was more marked in the cervix than in the fundus and midsegment (63 ml. per kilogram versus 28 and 24).

TABLE I

CASE NO.	CONDITION	H_2O CONTENT (ML./KG.) FUNDUS	MIDSEGMENT	CERVIX	ENDOMETRIUM
*Pieces of Myometrium of High Water Content.**—					
I	Early pregnancy (4 weeks)	822	821		852
VIII	Early pregnancy	836		848	829
IX	Early pregnancy	826	823	849	
III	Midcycle (15 days since last menstrual period)	862	830	859	856
V	Midcycle (9 days since last menstrual period)	830	823	841	861
Average		835	824	849	849
		±7	±2	±4	±7
Pieces of Myometrium of Low Water Content.—					
II	Second day of menstruation	806	804	791	(851)
IV	Prolonged uterine bleeding	811	801	783	814
VII	Prolonged uterine bleeding	805	795	783	808
Average		807	800	786	811
		±2	±3	±2	

*In Case VI, only endometrial scrapings were obtained.

The Electrolytes of the Uteri.—The average sodium and potassium contents for uteri classified according to their water content are shown in Table II. Two estimates of the extracellular space of these tissues have been included in Table II. These are based on the assumption that either the chloride content of the tissues is extracellular or that the sodium of the tissues is extracellular. The table also gives the total of sodium plus potassium concentration per liter of cell water. The plasma electrolyte analyses are presented in Tabe III.

Examination of the data in Table II reveals two main types of variation, namely, (1) variations between the two main groups of uteri as classified according to their water content or endometrial state, and (2) variations between the tissues from various areas of the same uteri.

TABLE II. ELECTROLYTES OF HUMAN UTERI

	ORIGINAL DATA					CALCULATED DATA				
	Na CONTENT (MEQ./KG. OF WEIGHT)		K CONTENT (MEQ./KG. OF WEIGHT)		Cl CONTENT (MEQ./KG. OF FRESH WEIGHT)	"EXTRACELLULAR" SPACE (Ml./KG.)		TOTAL Na + K (MEQ./L.)		
	FRESH	DRIED	FRESH	DRIED		Cl SPACE	Na SPACE	TISSUE WATER	CELL WATER (Cl)	CELL WATER (Na)
Uteri of High H_2O Content.—										
Fundus	68.7 ±2.1	419 ±14	54.5 ±4.1	335 ±22	70.1 ±4.8	556	492	147.7	148.4	159.8
Midsegment	86.8 ±8.7	490 ±50	60.5 ±4.6	359 ±22	62.5 ±6.0	487	621	178.8	240.7	541.5
Cervix	88.2 ±7.1	578 ±42	33.7 ±1.6	223 ±6	66.6 ±8.5	532	631	143.3	152.4	155.8
Endometrium	72.1 ±7.1	482 ±28	55.7 ±0.7	373 ±20	53.3 ±4.8	394	516	150.7	152.8	156.2
Uteri of Low H_2O Content.—										
Fundus	78.1 ±9.6	429 ±46	71.0 ±7.0	368 ±33	78.7 ±4.9	667	568	184.9	313.3	261.9
Midsegment	79.2 ±2.2	396 ±12	61.5 ±2.9	308 ±18	72.0 ±6.3	609	570	175.7	243.4	294.0
Cervix	98.7 ±6.6	460 ±26	30.6 ±3.3	143 ±17	73.0 ±5.0	619	712	164.8	258.0	1291.7
Endometrium	65.4	376	58.2	338	50.5	427	463	152.3	154.8	153.2

1. *Variation between uteri of different water content:*

A. The sodium content (in relation to dry weight) tended to be low in all uterine tissues of low water content except those from the fundus. This difference was highly significant for cervical pieces. These tissues did not have a low sodium content in terms of their fresh (wet) weight.

B. Cervical pieces of lower water content contained significantly less potassium when dry weight was taken as the basis for comparison.

C. Pieces of low water content generally had larger chloride spaces, and, in the case of fundus and cervix, larger sodium spaces as well.

D. All myometrial pieces from uteri of low water content, as well as midsegment myometrium from high water content uteri, had high calculated total cellular cation concentration, exceeding the extracellular concentration of these ions. Excess cation content in fundal and cervical myometrium of low water content also resulted when these were calculated[6] in terms of cellular water, using either chloride or sodium space as equivalent to the extracellular volume.

2. *Variation of electrolytes in relation to site of origin of the tissue in the uterus:* The differences in the electrolyte content of various parts of the uterus were surprisingly large for a tissue of relatively homogeneous structure. In both groups of uteri it is apparent that the fundus had a higher potassium and a lower sodium content than the cervix. Midsegment and endometrium were intermediate. The chloride space of the fundus was as large or larger than that of the cervix even though the sodium space is smaller. Midsegment and endometrium generally had smaller chloride spaces than either fundus or cervix.

TABLE III. PLASMA AND EXTRACELLULAR ELECTROLYTES OF HUMAN UTERUS

CASE NO.	MEQ./L. PLASMA			MEQ./L. EXTRACELLULAR WATER*
	Na	Cl	K	Na + K
Uteri of High H_2O Content.—				
I	136.3	117.0	4.8	142.4
III	136.6	115.7	2.0	140.2
V	137.2	115.0	3.4	142.1
VIII	152.1	111.0	3.0	156.8
IX	143.0	120.5	3.6	148.2
Uteri of Low H_2O Content.—				
II	136.1	105.5	4.45	142.1
IV	140.0	108.5	3.4	145.0
VII	143.5	110.8	2.8	148.0

*See methods for calculation.

Comment

Distribution of Sodium and Chloride.—The data indicate that neither chloride nor sodium is confined solely to the extracellular space of human myometrium. The chloride and sodium spaces shown in Table II represent the volume of fluid required to distribute the measured quantities of the ion in question at its concentration in extracellular fluid. If both these ions were distributed solely in extracellular fluid, their spaces would be equal. If one were distributed partly in cells and the other were solely extracellular, then the completely extracellular ion would have a voume of distribution or space smaller than the other. Actually, in some areas (e.g., fundus) the chloride space is larger than the sodium space while in other areas (e.g., cervix) the sodium space is larger.

Manery and Hastings[13] previously have pointed out that provided all ions are in solution there are sodium-containing cells in a tissue in which the volume of distribution of sodium is greater than that of chloride, and similarly that there must be chloride-containing cells in a tissue in which the volume of distribution of chloride is greater. Manery, Danielson, and Hastings[12] have shown that a greater chloride than sodium space is sometimes found in relatively acellular connective tissue, owing possibly to ion binding. However, histological examination of human uteri has shown no evidence of larger quantities of connective tissue in the chloride-rich fundus.[14] Therefore cells of fundal myometrium contain chloride while cervical myometrial cells contain sodium. In midsegment myometrium, chloride is present in cells in uteri of high water content, but cellular sodium is present in uteri of low water content.

Since the cell membrane is never an absolute barrier there are probably small amounts of both ions in all cells so that a relative excess of one proves only the presence of that ion but does not exclude the possible presence of the other. Although qualitative conclusions can therefore be drawn about cellular electrolytes from these data, quantitative estimations are not meaningful until an adequate measure of extracellular volume is devised. It seems very likely, however, that fundal cells do contain appreciable amounts of chloride. Their permeability characteristics must differ markedly from those of striate muscle[6] and the remainder of human uterine myometrium. Possibly the functional dominance of the fundus over other myometrial area[11] is related to this unusual permeability of fundal myometrium from uteri of high water content.

The Excess Cation in Myometrium.—The occurrence of an excessive total cation concentration in tissue water compared to the concentration in extracellular fluid is generally considered a result of the presence of polyvalent colloidal anions (protein, etc.) of low osmotic activity either in cells or in the extracellular phase.[6] The excess of cation (and anion) varies in different regions of the uterus, there being little or no excess in cervical myometrium and endometrium, a marked excess in myometrium from the corpus, and an excess in fundal myometrium, only in uteri of low water content. This latter difference from uteri of low water content may result from different levels of ovarian hormones.

Cervical Electrolytes.—The cervical myometrium contains more sodium and potassium per unit weight of dry solids in uteri of high water content. This difference does not appear when the same data are considered in relation to fresh weight. This difference therefore results chiefly from an increase in the content of electrolyte-containing tissue fluid relative to tissue solids.

In both groups of uteri the cervix contained less potassium and somewhat more sodium than the remainder of the myometrium. This would be expected from the relatively smaller proportion of cellular material and the larger proportion of extracellular material such as connective tissue in the cervical myometrium.[14]

Water and Electrolyte Concentrations and Ovarian Hormones.—The differences in water content, in electrolytes, and in extracellular space between pieces of myometrium from bleeding and nonbleeding uteri may have been the result of variations in the quantity or types of hormones acting on the uterus. Estrogens have been previously shown to increase uterine water content.[8] In the first or nonbleeding group (i.e., those with high water content) 3 uteri were removed in early pregnancy and 2 in midcycle. None had a history of prolonged uterine bleeding. These uteri presumably were under the influence of high blood levels of estrogen, and (except Case V) probably of progesterone as well. Two of 3 uteri with lower water content were removed because of

prolonged uterine bleeding. The third specimen (Case II) was taken on the second day of menstruation. These uteri probably were exposed to a lesser or deficient level of estrogen and progesterone which may account for the lower myometrial water content in these specimens. In so far as the different water content of the two groups of uteri can be attributed to variations in hormone levels, it appears that the sensitivity of the cervix to the influence of ovarian hormones is greater than that of the fundus and midsegment.

Changes in water content probably reflect in part dilution of cellular electrolytes in the myometrium under the influence of ovarian hormones rather than expansion of the extracellular space. This seems an almost inevitable conclusion from the fact the total water content increased while the "extracellular" spaces usually decreased (see Tables I and II). Dilution of cellular electrolytes also explains the decreased cellular content of sodium plus potassium (Table II) in pieces of higher water content.

Further data on electrolytes and water composition during various stages of the menstrual cycle, and a more adequate measure of the extracellular space will be necessary before quantitative estimates of the effects of the hormones on cellular concentrations of electrolytes can be made. However, these data strongly suggest that such differences exist and lend credibility to the hypothesis that hormones may affect uterine excitability by altering the previous cellular permeabilities to ions. Since the fundus is an area of greater excitability and automaticity in most cases[11] and also contains larger quantities of intracellular chloride, the possibility of a direct relationship between these properties and cellular permeability to chloride merits further investigation.

Summary

1. The sodium, potassium, chloride, and water contents of human myometrium and endometrium have been examined. The myometrium was divided so that muscle from the fundus, midsegment, and lower uterine segment or cervix could be analyzed separately.

2. Uteri were divided into groups according to whether or not they were bleeding at the time of hysterectomy. Specimens of myometrium from bleeding uteri were found to fall into a group with low water content, whereas those from nonbleeding uteri fell into a group with higher water content. In one case, the endometrium from a menstruating uterus was found to possess a high water content.

3. Electrolyte differences were found to be correlated with this difference in water content. Cervical myometrium with higher water content had more sodium and more potassium per kilogram dry weight. Other myometrial areas showed similar differences but these were not statistically significant. The chloride spaces were smaller in myometrium from uteri of high water content. The probability that these differences are due to differences in ovarian hormone levels was discussed.

4. Variation in electrolyte content occurred within both groups according to the source of the myometrium. In general, fundal myometrium contained less sodium and more potassium than cervical myometrium. Fundal myometrium also had a larger chloride space and evidence was adduced to show that a portion of this chloride is cellular. Intervening myometrium tended to show intermediate electrolyte patterns.

5. The evidence suggests that the observed variations are partly due to alterations in the intracellular water and electrolyte contents of myometrium. However, variations in connective tissue may contribute to variation between pieces of myometrium from various areas of the same uterus, and to differences

between pieces from the same area in different uteri. As a working hypothesis it is suggested that permeability of smooth-muscle cells to chloride is related directly to their excitability.

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IDENTIFICATION OF ALPHA-AMYLASE AS A SECRETION OF THE HUMAN FALLOPIAN TUBE AND "TUBELIKE" EPITHELIUM OF MÜLLERIAN AND MESONEPHRIC DUCT ORIGIN

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OVER seventy-five years ago Frommel[1] described two types of epithelium lining the Fallopian tube of the cat. One was a ciliated columnar cell and the other was a nonciliated columnar cell which he believed was secretory in nature. From the time of Frommel until the present, many investigators have confirmed and expanded his work in numerous animals, including man.[2-6]

Novak and Everett[7] in 1928 demonstrated morphologic cyclic changes of the epithelium in human Fallopian tubes in response to ovarian hormones. They suggested that a substance was secreted which was probably of nutritive value to the ovum.

Adequate morphologic evidence has been compiled to support the theory of a tubal secretion, but the identity of this secretion is still unknown.

In an attempt to elucidate the nature of this secretion, the following hypothesis is advanced: *The epithelium lining the Fallopian tube secretes an enzyme which has the ability to degrade glycogen to glucose. The probable physiologic substrate for this enzyme is the intraluminal glycogen produced by secretory endometrium.* A combined morphologic, embryologic, and enzymologic approach has been used to support this hypothesis.

An understanding of the embryologic development of the male and female genital duct system is necessary in order to understand why certain cystic structures were chosen for study. Early in the fifth embryonic week the tubules of the mesonephros appropriate the pronephric duct which was formed in the fourth embryonic week. This duct is now called the mesonephric duct and for a short time coexists in close proximity to the Müllerian duct. The former is destined to become the genital duct system of the male while a portion of the latter will develop into the Fallopian tubes of the female.

As the gonads differentiate into testes or ovaries, the appropriate duct system continues to develop while the other duct system atrophies. Occasionally a cystic vestige of the Müllerian duct is found attached to the tunica vaginalis of the testis and is called the hydatid of the testis. In the female pelvis, a number of cystic vestiges are commonly found which represent atrophic remnants of both the mesonephric and Müllerian ducts. These are diagrammatically shown in Fig. 1. The small cystic structures located in the broad ligament are known as epoophoron and paroophoron cysts. They are of mesonephric-tubule origin. A larger cyst located in the mesosalpinx and of

mesonephric duct origin is called a parovarian cyst. Cysts of Müllerian duct origin are found in the tube wall and are called Müllerian duct cysts. Other pedunculated cysts attached to the fimbriated end of the tube are called hydatids of Morgagni and are the female counterpart of the hydatids of the testis.

The lining epithelium of these cystic vestiges may vary from simple cuboidal cells to ciliated and nonciliated columnar cells which are morphologically identical to the epithelium lining the Fallopian tubes.

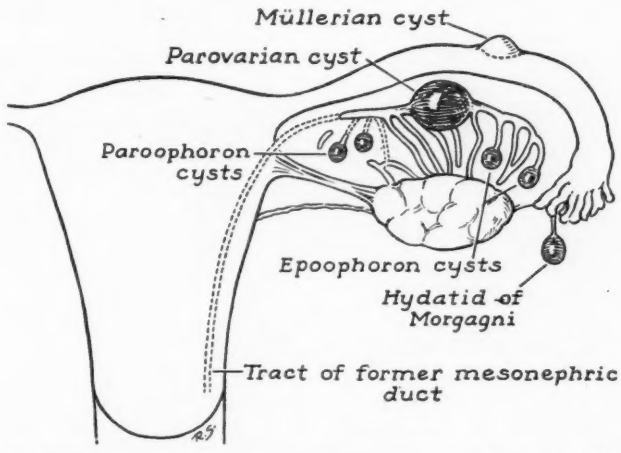

Fig. 1.—Diagram of cysts formed from the atrophic mesonephric duct, tubules and Müllerian duct.

Method

Fluid from 75 cystic structures lined by epithelium morphologically resembling that which lines the adult Fallopian tube was assayed for diastase enzyme activity. Somogyi's micro method for determining diastase activity in serum and biologic fluids was used. A diastase unit equals 1 mg. of reducing sugar per 100 c.c. of serum or fluid. Only epithelium composed of both ciliated and nonciliated columnar epithelium was considered as "tubelike" epithelium. The cystic structures were divided into five groups according to their anatomic location or embryologic origin. These are listed in Tables I-V.

A small number of cystic structures free from hemorrhage and from other embryologic origins such as breast cysts, physiologic ovarian cysts, omental cysts, and hydrocele-sac fluid were assayed for diastase activity.

Whenever excess cyst fluid was available after the diastase activity had been assayed, various chemical and physical precedures were performed to characterize the nature of this enzyme. These procedures are listed under Results.

Glycogen was extracted from endometrium by the method of Good, Kramer, and Somogyi.[9] This glycogen, as well as that commercially obtained, was then used for the substrate of enzyme obtained from cystically dilated Fallopian tubes.

Two sets of micro sections were prepared from secretory endometrium fixed in 10 per cent neutral formalin. One set of control micro sections was incubated in a phosphate-sodium chloride buffer at pH 8.6 for 30 minutes, and the second set of micro sections was incubated with buffer and tubal enzyme. Both sets were stained by the Bauer-Feulgen technique as modified by Lillie[10] for the demonstration of glycogen.

Results

Table I: Fluid from 22 cysts of mesonephric tubule origin located in the mesosalpinx is included in this table. They include both paroophoron and epoophoron cysts. The minimum activity was 1,800 diastase units; maximum activity 32,000 units, with an average activity of 10,100 diastase units.

TABLE I. FLUID FROM PAROOPHORON AND EPOOPHORON CYSTS (MESONEPHRIC TUBULE ORIGIN)

CASE NO.	AGE OF PATIENT	AMOUNT OF FLUID IN CYST (C.C.)	ENZYME ACTIVITY OF CYST FLUID IN DIASTASE UNITS
10	46	0.40	1,800
12	39	0.25	12,000
13	42	0.35	10,000
14	38	0.20	1,800
15	38	0.45	8,000
17	40	0.35	16,000
23	28	0.25	11,000
24	38	0.15	21.000
26	36	0.35	1,800
27	41	0.20	2,000
28	43	0.10	4,000
29	40	0.40	18,000
30	38	0.35	9,000
31	37	0.20	22,000
39	38	0.15	1,900
43	34	0.25	2,000
44	36	0.25	24,000
45	42	0.35	32,000
47	28	0.15	15.000
49	36	0.20	3,500
51	39	0 25	3.200
59	48	0 30	2,800

Table II: Diastase activity of fluid from 6 cysts of mesonephric duct origin located between the leaves of the broad ligament is included in this table. These are large parovarian cysts. Minimum diastase activity was 1,100 units; maximum activity 2,800 units, with an average of 1,600 units.

TABLE II. LARGE PAROVARIAN CYSTS

CASE NO.	AGE OF PATIENT	AMOUNT OF FLUID IN CYST (C.C.)	ENZYME ACTIVITY OF CYST FLUID IN DIASTASE UNITS
4	25	150	1,400
18	36	90	1,800
34	40	160	2,800
56	38	200	1,600
66	42	350	1,200
70	32	110	1,100

TABLE III. FLUID FROM HYDROSALPINX

CASE NO.	AGE OF PATIENT	AMOUNT OF FLUID IN CYST (C.C.)	ENZYME ACTIVITY OF TUBAL FLUID IN DIASTASE UNITS
1	32	14	8,000
2	38	8	1,200
3	49	5	10,000
25	46	32	2,000
48	38	80	6,000
52	44	60	1,600
67	50	120	3,500
72	38	10	2,000

Table III: Diastase activity of fluids from 8 cystically dilated Fallopian tubes showing no histologic evidence of active inflammation is included in this table. Minimum diastase activity was 1,200 units; maximum 10,000 diastase units with an average activity of 4,300 units.

Table IV: Diastase activity of fluid from 23 hydatids of Morgagni, Müllerian duct origin, is included in this table. The minimum activity was 1,800 units, maximum activity 32,000 diastase units, with an average activity of 8,400 units.

Fig. 2.

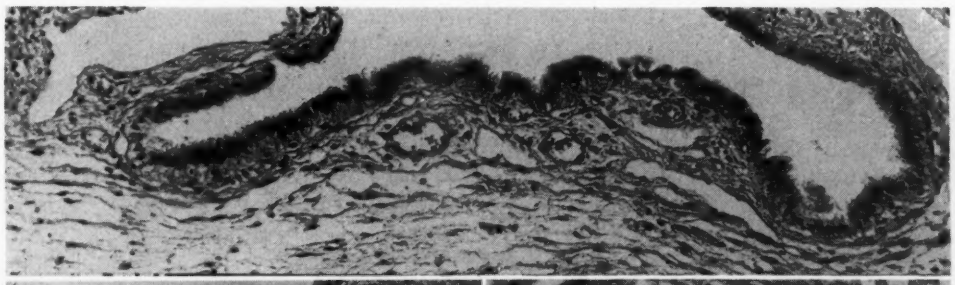

Fig. 3.

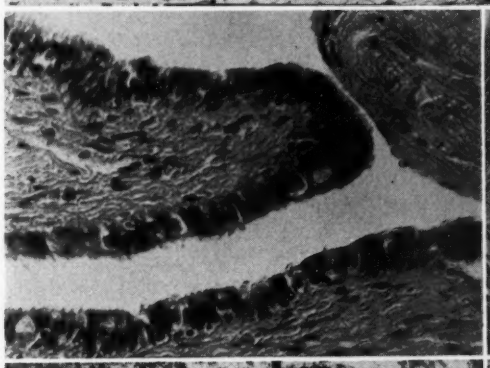

Fig. 4

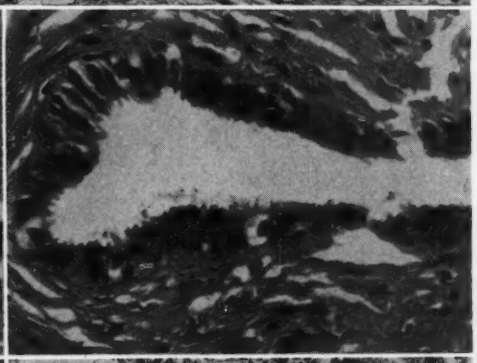

Fig. 5.

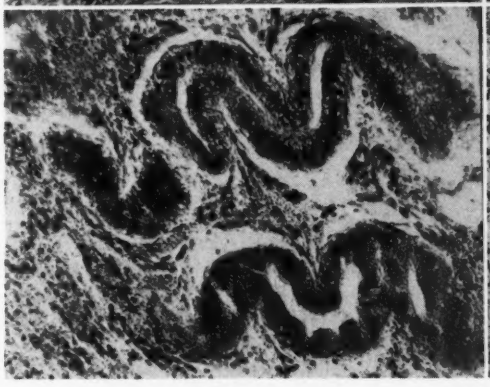

Fig. 6.

Fig. 2.—Photomicrograph of epithelium from a hydrosalpinx. Fluid assayed 10,000 diastase units.

Fig. 3.—Photomicrograph of epithelium lining a hydatid of the testis. Fluid assayed 80,000 diastase units.

Fig. 4.—Photomicrograph of epithelium lining a Müllerian duct cyst. Fluid assayed 64,000 diastase units.

Fig. 5.—Photomicrograph of secretory endometrium incubated 30 minutes in buffer and stained for glycogen as described under Method.

Fig. 6.—Photomicrograph of an adjacent serial micro section of endometrium incubated the same length of time in buffer-enzyme solution showing a marked decrease in endometrial glycogen.

TABLE IV. FLUID FROM CYSTS OF MORGAGNI (MÜLLERIAN DUCT ORIGIN)

CASE NO.	AGE OF PATIENT	AMOUNT OF FLUID IN CYST (C.C.)	ENZYME ACTIVITY OF CYST FLUID IN DIASTASE UNITS
7	23	0.25	2,000
9	38	0.20	1,800
11	28	0.15	2,800
19	42	0.25	2,200
21	47	0.30	3,200
32	54	0.15	1,800
35	36	0.30	3,200
36	39	0.20	18,000
38	41	0.15	3,800
40	29	0.25	4,200
42	32	0.40	12,000
46	42	0.15	32,000
53	37	0.25	3,400
55	36	0.20	12,000
57	38	0.40	14,000
58	49	0.35	6,000
60	27	0.15	2,000
63	52	0.25	16,000
64	34	0.10	28,000
69	35	0.20	3,500
71	42	0.20	10,000
73	46	0.15	8,000
75	48	0.30	3,500

TABLE V. FLUID FROM MÜLLERIAN CYSTS ON OR WITHIN THE TUBE WALL

CASE NO.	AGE OF PATIENT	AMOUNT OF FLUID IN CYST (C.C.)	ENZYME ACTIVITY OF CYST FLUID IN DIASTASE UNITS
6	28	0.10	52,000
8	39	0.15	24,000
16	36	0.10	36,000
20	34	0.08	18,000
22	36	0.10	32,000
33	35	0.15	24,000
37	42	0.05	16,000
41	38	0.20	64,000
50	39	0.15	24,000
54	27	0.10	22,000
62	49	0.25	38,000
68	26	0.10	40,000
74	48	0.05	28,000

Table V: Diastase activity of fluid from 13 cysts of Müllerian duct origin located on or within the Fallopian tube wall is included in this table. Several of these cysts were interpreted as cystic tubal diverticula. The minimum diastase activity was 16,000 units; maximum activity 64,000 diastase units, with an average activity of 32,000 diastase units.

Two hydatids of the testis which are of Müllerian duct origin and are male counterparts of the hydatids of Morgagni in the female, were not included in a table. The fluid from one assayed 60,000 diastase units and the other 80,000 units. (Fig. 3).

Serum diastase levels were determined in 25 patients, from whom cysts were obtained, and found to be within the physiologic level of 80 to 150 diastase units by the same method as used to determine diastase activity of cyst fluid. Examination of the histories from each of the patients from whom cyst fluid was obtained disclosed no history of acute pancreatitis or cholecystitis.

The following physical and chemical properties of the enzyme were demonstrated:

1. It is protein in nature and migrates by electrophoresis with a mobility of approximately –5.7 times 10^{-5} in diethylbarbiturate buffer at pH 8.6.
2. It can be dialyzed against distilled water. After dialysis it is inactive, but can be reactivated by the addition of chloride ions.
3. At 0° C. it is soluble in 50 per cent acetone and insoluble in 70 per cent acetone.
4. It will split alpha 1-4 glucosidic bonds in both starch and glycogen.
5. It will not liberate inorganic phosphate nor synthesize glycogen from glucose-1 phosphate.
6. It shows no alkaline or acid phosphatase activity.

Glycogen extracted from secretory endometrium was degraded by the enzyme. Also micro sections of secretory endometrium were prepared and treated as described under Method. The marked decrease in PAS-positive material in sections incubated in enzyme was interpreted as degradation of glycogen (Figs. 5 and 6) by the enzyme.

Comment

Fluid from cystically dilated human Fallopian tubes, cystic vestiges of mesonephric tubules and ducts, and Müllerian ducts, all lined by tubal or "tubelike" epithelium, contained a diastase enzyme which varied in concentration from 10 to 700 times that of the serum diastase level. There are only two explanations for this: (1) this type of epithelium secretes the enzyme into the lumen fluid; or (2) this type of epithelium has a selective permeability which allows the transfer of the enzyme from the serum into the lumen fluid against a concentration gradient shown to be as high as 700-fold. Either of these mechanisms would involve work by the epithelium and therefore represents secretory activity by the epithelium.

The specific concentration of enzyme in various cysts depends on four factors: (1) the number of secretory cells in relation to nonsecretory cells and undifferentiated cells; (2) the length of time which the cells have been secreting; (3) the total volume of fluid making up the cyst; and (4) the stability of the enzyme. Therefore, the significance of this study depends on the demonstration that a specific enzyme is secreted by tubal, mesonephric, and Müllerian duct epithelium rather than specific values which are recorded for the various cysts.

The physiologic significance of these findings is not known. However, it was shown that glycogen derived from secretory endometrium could be degraded from a polysaccharide, which is in a poorly usable form by cells, to glucose which is easily metabolized by cells. This fact, plus the morphologic evidence that a considerable amount of tubular secretion is formed during the passage of the ovum through the tube, and during the premenstrual phase, lends support to the hypothesis that the physiologic substrate for this tubal enzyme may be the glycogen produced by secretory endometrium.

Two theoretical advantages can be cited in support of such a hypothesis: (1) The ovum would have available glucose for nutrition prior to becoming

self-sufficient with the development of trophoblasts. (2) High ovum implantation would be favored because of a higher available glucose concentration in the fundus where the tubal enzyme would be found in highest concentration.

From the physical and chemical characteristics listed under Results it is most likely that this enzyme is an alpha-amylase. It is of interest to note that only extracellular glycogen is degraded by amylases in the human being while intracellular glycogen is metabolized by phosphorylase. This fact would also support the concept that endometrial intraluminal glycogen is the physiologic substrate for the enzyme.

No enzyme was demonstrated in 3 cysts from preadolescent girls. This is not a sufficient number of determinations to establish whether this is a constant finding or not; but if it proves to be a consistent finding, then it would be justifiable to assume that the secretion of this enzyme by the tubal epithelium is influenced by ovarian hormones.

Summary

1. Fluid from 75 cystic structures of Müllerian duct, mesonephric duct, and tubule origin which were lined by Fallopian tube epithelium or epithelium morphologically identical with that of Fallopian tube mucosa was assayed for diastase activity.

2. The diastase enzyme activity of fluid from the above cysts varied from a minimum of 1,100 diastase units to a maximum of 80,000 units.

3. The chemical and physical behavior of this enzyme leads to the conclusion that it is most likely an alpha-amylase.

4. The hypothesis is advanced that *the epithelium lining the Fallopian tube secretes an enzyme which has the ability to degrade glycogen to glucose. The probable physiologic substrate for this enzyme is the intraluminal glycogen produced by secretory endometrium.*

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AN INVESTIGATION OF TUBAL IMPLANTATION FOR CORNUAL BLOCK

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THERE have recently been considerable discussion and interest about the repair of bilateral cornual block by tubal implantation. Reports have been published[1-5] of high rates of conception following this operation. The techniques recommended involve some form of boring, or coring, through the cornu and implanting the proximal portion of the tube, previously strung with a tube or rod of polyethylene, into this artificially formed tunnel. This polyethylene rod is removed from within the tunnel in the following three to twelve weeks.

The experience with this operation at the Samaritan Hospital for Women has been sadly at variance with all published figures seen and may be of some interest.

To evaluate this procedure, 1,830 consecutive case records from our infertility clinic were taken, covering the years 1948 to 1955. All records showing bilateral cornual occlusion on hysterosalpingography at one or more tests were set aside for investigation. There was a total of 240 cases. Cases of reopening of normal tubes that had previously been tied as a deliberate sterilizing procedure were not included in this series. A letter was sent to each patient. Our usual response to letters of enquiry sent to patients over the last five years has been about 60 to 65 per cent. In this instance the response was much greater and 209 patients either wrote or appeared at our clinic.

Here follows the fate of these 209 patients. Twenty-seven wrote that they had had one or more pregnancies since their last hysterosalpingogram. This reduced the number of cases for further investigation to 182. Thirty-three patients wrote or came to say that they no longer desired further investigation as they were "too old," "too tired," widowed, separated, divorced, or that social circumstances had changed since their last visit. This left a residuum of 149 cases.

In every case the endometrial biopsy showed a normal secretory endometrium and no cases fell by the wayside on this account.

Our standard of subfertility in the male on the basis of semen analysis was less exacting than many; nevertheless, even with a generous interpretation in favor of the patient, 14 cases of oligospermia were found where the sperm count and morphology ruled out any reasonable prospect of conception. This reduced the number of our cases to 135. A further 11 cases showed complete

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azoospermia, reducing our numbers to 124. One case was discarded as intercourse now took place only once a year and one case as intercourse took place every six months. Our number was now 122.

It was decided to operate on each of these patients if they showed no patency at two insufflations and bilateral cornual block on two more hysterosalpingograms.

At repeat insufflation, 26 were found to have one or both tubes patent, reducing our number to 96. At repeat hysterosalpingography 22 showed one or both tubes patent, reducing our number to 74; and a further 24 cases now showed a block not at the cornua but this time at the ampullary ends. We now had 50 cases.

This final group of hardy patients were again interviewed, and it was explained that we proposed operating on them. Our plan was to do a final insufflation under anesthesia and if this showed no passage of carbon dioxide a laparotomy would be done. On opening the abdomen a retrograde insufflation would be done, and if this showed bilateral cornual block then a repair would be undertaken. A picture of minimal mortality rates was presented, but no assurance of success in rendering the tubes patent, or of pregnancy inevitably following should the tubes be made patent was given. Six patients refused operation when we could give no absolute guarantee of success. This reduced our number to 44.

Over a period starting in October, 1952, and ending in July, 1955, these 44 patients were admitted to hospital. All of these dauntless women had had at least one endometrial biopsy, two and usually more hysterosalpingograms showing bilateral cornual block, and two or more unsuccessful insufflations with or without anesthetic.

At final insufflation under anesthesia prior to laparotomy 26 of these patients were found to have one or both of their tubes patent and were discharged home. The remaining 18 patients did undergo laparotomy. Five of these were found to have both tubes clearly patent on retrograde insufflation and the abdomen was closed. At this stage 15 patients remained. Four of these were found to have both tubes completely disorganized along their whole length by old inflammation. In 2 of these it was necessary to do a bilateral salpingectomy, while in the other 2 cases a combined salpingostomy with cornual implantation with little or no hope of success was performed. Our numbers were reduced to 9.

The remaining 9 patients had bilateral cornual occlusion with the remainder of the tube clinically normal in appearance and patent as far as the cornua on retrograde insufflation. Five surgeons using 3 slightly varying techniques with polyethylene operated on these 9 patients and implanted the tubes into the cornua. There were no deaths. The postoperative morbidity rate was nil. The polyethylene tubes were removed in from three to twelve weeks, usually the latter.

A hysterosalpingogram was done on each of these cases three to six months after the polyethylene tubes were removed. In 8 cases the films showed bilateral cornual block. In one case the tubes were shown as patent. We did

not repeat this or any other test for patency as the ordeals of these patients had already almost amounted to martyrdom, and our experience as to the reliability of these tests when negative, as evidenced in this series, was not such as to give us confidence in their value. By May, 1956, there was no record of any pregnancy.

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A STATISTICAL COMPARISON OF THE THERAPEUTIC VALUE OF CARBON DIOXIDE INSUFFLATION VERSUS OIL SALPINGOGRAPHY*

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PUBLISHED impressions of many investigators in the infertility field have led to the use of many procedures and medications which have little or no established therapeutic value. This is to be expected in that there are still unknown factors responsible for the infertility of many couples. It is also true that many couples conceive after long periods of infertility for no apparent reason. In our clinic such unexplained conceptions account for about one-third of all the pregnancies.[1] Any method of evaluating the therapeutic effect of a procedure must make allowance for these unexplained conceptions. Evaluation by careful statistical measures of the treatment of infertility problems is rare in the literature. The purpose of this study is to evaluate and compare the therapeutic effects, if any, of the carbon dioxide insufflation procedure and salpingography in patients with normal tubal patency.

Material

For interpretive purposes, uniformity in the selection of cases is of great importance. For this study, only couples with no major defects which might cause infertility were included. Many of these couples had been unsuccessfully treated by other physicians prior to admission to our clinic. To be acceptable, the couples had to meet certain definite requirements which are as follows:

Man and Woman.—

1. The consistent effort to achieve pregnancy must have been made for a minimum period of one and a half years prior to being accepted for study.
2. By complete history and physical examination, both the man and the woman must have been healthy, with no significant disease that might affect their fertility status.
3. The laboratory tests, blood counts, urinalysis, and serological test for syphilis, must have been normal for both.
4. Normal coitus must have been performed at least six times per month.
5. No other definitive therapy which could have brought about conception was given during the periods covered by the statistical comparisons.

Man.—

1. The urological examination must have been normal.
2. The sperm count must have been 60 million or more per cubic centimeter.
3. At least 60 per cent of the sperm must have been motile at the end of one hour.

*A grant from the Brush Foundation of Cleveland, Ohio, made this study possible.

Woman.—

1. The menstrual cycle must have been regular, 25 to 35 days.
2. The basal body temperature charts must have shown a characteristic ovulatory curve in the majority of cycles recorded.
3. The Huhner test at the end of four or more hours must have been positive.
4. The pelvic examination must have shown a normal uterus and ovaries. All women with fibroids, large ovarian cysts, or a history of pelvic surgery other than a curettage were eliminated. Also women with a definite history of pelvic inflammatory disease were rejected.
5. Normal tubal patency must have been present.

Normal tubal patency was considered to be present if the CO_2 insufflation test was positive or if the salpingograms showed free passage of oil into the peritoneal cavity. A negative CO_2 insufflation test was not considered a cause for rejection if subsequent salpingography was normal. All insufflation tests were done while the patient was conscious. Pressures over 200 mm. Hg were never used. Only patients who experienced immediate shoulder pain on sitting up were considered to have a positive test. All cases of abnormal salpingography were rejected. These were the ones which showed: (1) nonfilling of one or both tubes, (2) complete distal block of one or both tubes, or (3) passage of some oil into the peritoneal cavity but definite pocketing of part of the oil at the distal end of one or both tubes at the end of 24 hours. Iodochloral and Lipiodol were the only agents used and three plates were routinely taken; 24 hour plates were obtained in all doubtful cases.

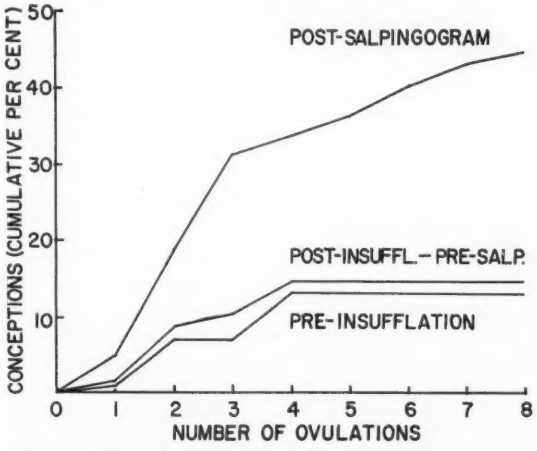

Fig. 1.—The curves of the cumulative probability of conception by ovulations of the preinsufflation, the postinsufflation presalpingogram, and postsalpingogram periods.

CO_2 insufflations were done two to four days before an expected ovulation. Salpingography was done in the preovulatory part of the menstrual cycle.

If pregnancy occurred prior to completion of tests to establish the criteria above, those not done were considered to be normal. Selection was from 514 couples studied consecutively in the Infertility Clinic at the Maternal Health Association of Cleveland, Ohio, according to the minimal standards established by the American Society for the Study of Sterility.[2] Only 100 of these couples were found to meet our criteria and were used in this study. Eighty of these 100 couples had been treated for their infertility prior to admission to the clinic.

Method

If CO_2 insufflation and salpingography have no specific therapeutic value, then the rates of conception should be the same before insufflation, after insufflation but before salpingography, and after salpingography. If one of these

procedures is of therapeutic value, then the rate of conception should show an increase subsequent to the procedure. Each couple's time in the study has therefore been divided into three periods designated as follows:

1. *The Preinsufflation Period.*—The time from entering observation (the initial interview) in the clinic until the earliest of the five following events occurred: (a) conception; (b) CO_2 insufflation, positive or negative; (c) salpingography; (d) curettage or other major specific therapy; (e) observation discontinued or discharge from the clinic.

2. *The Postinsufflation Presalpingograms Period.*—The time from the first positive CO_2 insufflation until the earliest of four following events occurred: (a) conception, (b) salpingography, (c) curettage or other major specific therapy, (d) observation discontinued or discharge from the clinic.

3. *The Postsalpingogram Period.*—The time from the first salpingogram until the earliest of the three following events occurred: (a) conception, (b) curettage or other major specific therapy, (c) observation discontinued or discharge from the clinic.

The length of exposure to the risk of conception is measured by the number of ovulations within each period; and the rate of conception is measured by the cumulative probabilities of conception from the start of each period up to each (first, second, etc.) ovulation. These probabilities are computed from a life table constructed in a manner similar to that described, for example, by Merrell and Shulman.[3]

From the proportion that conceive at a given ovulation, the probability of conception in that cycle can be computed. Table I gives the data for the preinsufflation period. The computations to determine the cumulative probability of conception by each ovulation in that period of time are carried out as follows:

1. Of the 100 women entering the study and before the first ovulation for each occurred, 3 had a positive CO_2 insufflation, 2 had a negative CO_2 insufflation, and 1 had a salpingogram. So by the time that the first ovulation occurred, 6 of these 100 women had had procedures carried out and were therefore not exposed to the risk of conception during the preinsufflation period.

2. At the time of the first ovulation, 94 women remained who could have conceived. One did conceive. Before the second and after the first ovulation, 23 women had positive insufflation tests, 3 had negative insufflation tests, and none had a salpingogram. Thus by the time of the second ovulation, 94 less 1, less 23, less 3, or 67 women remained who could possibly conceive during the presinsufflation period.

3. At the first ovulation the proportion of women who did conceive was 1/94 or 0.0106 and the proportion who did not conceive was 93/94 or 0.9894. The cumulative probability of conception from the initial interview to the first ovulation is 0.0106.

4. As shown above, at the second ovulation 67 of the women in this group could have conceived and 4 did so. Thus 4/67 or 0.0597 of the women who had second ovulations conceived at them. The proportion of women who had second ovulations without conception is 63/67 or 0.9403. The cumulative probability of not conceiving by the second ovulation is obtained by multiplying the cumulative probability of not conceiving by the first ovulation by the proportion of women who had second ovulations without conception 0.9894 times 0.9403 or 0.9303. Subtracting this from 1.0000 gives the cumulative probability of conception by the second ovulation after the initial interview, 0.0697.

5. The cumulative probability of not conceiving from the initial interview to each subsequent ovulation is arrived at by multiplying the proportion who had the ovulation without conception by the cumulative probability of not conceiving by the preceding ovulation. By subtracting this product from 1.0000 the cumulative probability of conception by that ovulation is obtained.

Table I shows the data and computed probabilities for the time interval from the initial interview until another specific event occurred or for what has been designated as the preinsufflation period. Table II shows the data and computed probabilities for the time interval designated as the postinsufflation presalpingogram period and Table III for that designated the postsalpingogram period. The curves of the cumulative probability of conception for each of these three periods of time are graphically shown in Fig. 1.

TABLE I. COMPUTATION OF PROBABILITY OF CONCEPTION DURING PREINSUFFLATION PERIOD

OVULATION AFTER INITIAL INTERVIEW	PATIENTS AVAILABLE FOR CONCEPTION	CONCEPTIONS AT THIS OVULATION	PATIENTS ELIMINATED BEFORE NEXT OVULATION	PROPORTION CONCEIVING AT THIS OVULATION	CUMULATIVE PROBABILITY OF CONCEPTION
0*	100	-	6	-----	-----
1	94	1	26	0.0106	0.0106
2	67	4	25	0.0597	0 0697
3	38	0	23	0.0000	0.0697
4	15	1	6	0.0667	0.1317
5	8	0	2	0.0000	0.1317
6	6	0	2	0.0000	0.1317
7	4	0	0	0.0000	0.1317
8	4	0	0	0.0000	0.1317

*Initial interview.

TABLE II. COMPUTATION OF PROBABILITY OF CONCEPTION DURING POSTINSUFFLATION PRESALPINGOGRAM PERIOD

OVULATION AFTER POSITIVE CO_2 INSUFFLATION	PATIENTS AVAILABLE FOR CONCEPTION	CONCEPTIONS AT THIS OVULATION	PATIENTS ELIMINATED BEFORE NEXT OVULATION	PROPORTION CONCEIVING AT THIS OVULATION	CUMULATIVE PROBABILITY OF CONCEPTION
0	--	-	--	-----	-----
1	75	1	8	0.0133	0.0133
2	66	5	8	0.0758	0.0881
3	53	1	10	0.0189	0.1053
4	42	2	11	0.0476	0.1479
5	29	0	4	0 0000	0.1479
6	25	0	3	0.0000	0.1479
7	22	0	6	0.0000	0.1479
8	16	0	1	0.0000	0.1479

TABLE III. COMPUTATION OF PROBABILITY OF CONCEPTION DURING POSTSALPINGOGRAM PERIOD

OVULATION AFTER SALPINGOGRAPHY	PATIENTS AVAILABLE FOR CONCEPTION	CONCEPTIONS AT THIS OVULATION	PATIENTS ELIMINATED BEFORE NEXT OVULATION	PROPORTION CONCEIVING AT THIS OVULATION	CUMULATIVE PROBABILITY OF CONCEPTION
0	--	--	-	-----	-----
1	80	4	0	0.0500	0.0500
2	76	11	1	0.1447	0.1875
3	64	10	1	0.1562	0.3144
4	53	2	1	0.0377	0.3402
5	50	2	2	0.0400	0.3666
6	46	3	0	0.0652	0.4079
7	43	2	2	0.0465	0.4354
8	39	1	1	0.0256	0.4499

Results

The curve of the cumulative probability of conception for the preinsufflation period is practically identical with the curve for the postinsufflation presalpingogram period. The slight difference is not statistically significant. These findings indicate that in this group of cases CO_2 insufflation apparently had no

greater therapeutic value than exposure to the usual clinic routines. On the other hand, the curve of the cumulative probability of conception for the postsalpingogram period is significantly higher than the other curves, most of the increase coming at the second and third ovulations. The chances of conception by the fourth ovulation in the preinsufflation period and in the postinsufflation presalpingogram period are approximately 1 in 10, whereas in the postsalpingogram period they are about 1 in 3. Thus in our couples with no apparent defects and with normal tubal patency, CO_2 insufflation did not appear to enhance or increase the probability of conception, whereas salpingography definitely did.

It must be noted that these findings apply to the whole group of 100 couples. There were 33 women in the group who had not had a CO_2 insufflation or a salpingogram before coming to our clinic. Among these women the probability of conceiving in the postinsufflation presalpingogram period was greater than in the preinsufflation period. Although the difference was not significant, it suggests that the first CO_2 insufflation may have a therapeutic effect on some women. Our data do indicate that for women who have not benefited by one or more previous insufflations, another CO_2 insufflation does not have therapeutic value.

Comment

The diagnostic value of the CO_2 insufflation test is so well established that in the service of our patients it was felt that the insufflation should precede the salpingography. For this reason, a controlled study, with randomized treatment order, was considered not feasible. Because these patients entered and left these periods at different times and also remained in each period for varying lengths of time, the life table method of analysis was used.

As shown in our earlier report[4] and in this study with many additional cases, the therapeutic value of oil salpingography appears to be established. The mechanism of this beneficial effect is not clearly understood. Several possibilities were presented before but the evidence is still insufficient to determine even the most likely one.

Therapeutic effects have been attributed to the passage of CO_2 gas through apparently normally patent Fallopian tubes,[5] by: (1) forcing out mucous plugs and inspissated material, (2) separating obstructing agglutinations in the lumen of the tubes, and (3) actually separating fine adhesions at the fimbria. None of these processes has actually been observed in vivo at operation. In addition, the mechanism by which the ovum, free in the abdominal cavity, enters and passes down the tube is not known. Because the Fallopian tubes contain longitudinal and circular muscle fibers and because peristaltic activity of the tube has been observed in vivo, this muscular activity probably maintains tubal patency. Free activity of the fimbria is probably an important factor in the passage of the ovum into the tube. Any pathological condition such as adhesions which inhibits this freedom of fimbrial activity probably greatly reduces the chances of the ovum entering the tube but does not necessarily prevent its occurrence as long as an ostium is present.

The rise in pressure of the injected gas or oil may induce spasm of the uterine or tubal musculature in some instances. Therefore one or two negative tests do not establish the definite presence of tubal obstruction. Subsequent tests may be entirely normal. This is not unusual with CO_2 insufflation but is

less likely to occur with oil salpingography. Although actual proof is lacking, we do not feel that the passage of either gas or oil in any of our cases actually opened or improved the patency of the tubal lumen or ostium.

Although this study apparently indicates that the CO_2 insufflation test in this whole group has little or no therapeutic value in the presence of normally patent tubes, the diagnostic value of the test is certainly of utmost importance in the study of the infertile couple. The excellent diagnostic distinctions attained by Rubin[5] are of inestimable value. However, the interpretation of the kymographic findings are in many instances complicated and difficult.

Like many investigators, we believe that passage of gas with shoulder pain indicates only that patency exists between the cervical os and the abdominal cavity. In all cases of doubtful patency, oil salpingography is relied upon to determine the presence or absence of tubal abnormality.

For therapy, salpingography is not performed by us until complete studies are done and until it is felt that maximum therapeutic effect can be attained from the procedure, either alone or in conjunction with the treatment of other defects. The CO_2 insufflation test should certainly not be abandoned but should be used as a safe and simple screening diagnostic test. The oil salpingography should be used primarily for its therapeutic value and not as a diagnostic test except when the CO_2 insufflation test is negative or doubtful.

Conclusions

1. The probabilities of conception occurring for three periods of time, (a) pre-CO_2 insufflation, (b) postinsufflation presalpingogram, and (c) postsalpingogram in 100 selected infertile couples with no apparent defects have been determined and presented.

2. In the group studied, most of whom had had previous CO_2 insufflations without conception, CO_2 insufflation was not demonstrated to have therapeutic value. There was, however, some indication that initial CO_2 insufflation may have therapeutic value.

3. Oil salpingography was again demonstrated to have apparent therapeutic value.

4. In the study and treatment of the infertile couple:

A. CO_2 insufflation should be used primarily as a screening diagnostic test.

B. Oil salpingography should be used for diagnosis when the CO_2 insufflation test is negative or doubtful.

C. Oil salpingography should be employed for therapy when all the data have been collected and its maximum therapeutic effect can be attained either alone or in conjunction with other treatment.

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THE FAMILIAL OCCURRENCE OF ENDOMETRIOSIS

Report of Five Instances and Review of the Literature

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THE purpose of this paper is to direct attention to a thus far rarely mentioned etiological aspect of endometriosis, i.e., familial susceptibility. Five instances of familial occurrence will be reported and thirteen instances recorded in the literature are reviewed.

In none of the various theories concerning the etiology of endometriosis, which will not be discussed here since they have been recently reviewed by Gruenwald,[1] Seitz,[2] Ranney,[3] Gardner,[4] Javert,[5] and Petri[6] has there been any mention of or reference to familial susceptibility. The first such reference was made by Goodall[7] in 1943, who wrote: "this ground is almost virginal, so one treads warily and with some awe. However, there are facts which taken singly have no weight, but when taken collectively deserve some recognition. Familial tendencies seem to play a part. In my experience there have been decided family incidences." He then reported on five such instances, which he encountered on his service and ended his short observation: "It may be contended that these cases would fall within the law of chance. That is admitted, but it is worthy of study." With this remark in mind we checked closely the family history of all patients operated upon on our service for pelvic endometriosis. In a study* of 100 white and 10 Negro women with proved pelvic endometriosis encountered during the 5 year period 1950-1954, we found 5 such instances, each one occurring in sisters (10 patients). An extensive search of the world literature and review of more than 500 papers on endometriosis published since 1921 disclosed a total of only 13 instances reported by 4 authors: Goodall,[7] 5; Barnes,[8] 1; Henriksen,[9] 1; Gardner,[4] 6, to which we can add 5 instances, bringing the total to 18.

Analysis of Present Series of 5 Cases

The clinical and pathological findings in our 5 instances are summarized in Table I. The correct preoperative diagnosis was made in 4 of the 10 patients. It is noteworthy that in Sister No. 2, Case 1, the making of a correct preoperative diagnosis was definitely facilitated by the knowledge of proved pelvic endometriosis in Sister No. 1, 2 years previously. The average age at operation was 37 years. Four patients were private, 6 semiprivate. Nine patients were married and only 1 had used contraceptives. Six patients were absolutely or relatively sterile. Three of these, however, underwent previous salpingectomy for specific salpingitis and hemosalpinx. Proved venereal infection was present in

*Doctoral dissertation submitted to the Postgraduate School, Faculty of Medicine, University of Amsterdam, Netherlands, in partial fulfillment of the requirements for an advanced doctorate in medicine.

TABLE I. CLINICOPATHOLOGICAL FINDINGS IN FIVE INSTANCES OF FAMILIAL ENDOMETRIOSIS

	CASE 1		CASE 2		CASE 3		CASE 4		CASE 5	
	SISTER NO. 1	SISTER NO. 2	SISTER NO. 1	SISTER NO. 2	SISTER NO. 1	SISTER NO. 2	SISTER NO. 1	SISTER NO. 2	SISTER NO. 1	SISTER NO. 2
Year	1950	1952	1951	1953	1952	1953	1953	1954	1947	1954
Age at operation	37	42	46	35	41	38	33	37	26	34
Private patients	x	x	x	x	–	–	–	–	–	–
Semiprivate patients	–	–	–	–	x	x	x	x	x	x
Married	x	x	x	–	x	x	x	x	x	x
Single	–	–	–	x	–	–	–	–	–	–
Number of children	2	3	2	0	0	1	1	0	0	0
Number of miscarriages	–	1	–	–	–	–	–	–	–	–
Precautions used	–	–	–		x	–	–	–	–	–
Duration marriage—first child	9 months	2 years	9 months		–	5 years	9 months	–	–	–
Tubes open	Hemosalpinx	x	x	x	Hydrosalpinx	–	Hemosalpinx	–	–	–
Duration of symptoms preoperatively	8 months	8 months	2 months	–	3 months	1 year	5 years	4 years	10 years	2 days
Chief complaint	Abdominal pain	Abdominal pain	Menorrhagia	None	Menorrhagia	Menorrhagia	Abdominal pain	Sterility	Dysmenorrhea	Abdominal pain
Menorrhagia	x	–	x	–	x	x	–	–	–	x
Metrorrhagia	–	–	–	–	x	x	–	–	–	–
Dysmenorrhea	–	–	–	–	–		–	–		
Dysmenorrhea lifelong						x			x	x
Dyspareunia	–	–	–	–	–	x	–	x	x	x
Rectal complaints	–	–	–	–	–	x	–	–	–	–
Bladder involvement	–	–	–	–	–	x	–	–	–	–
Abdominal pain	x	x	–	–	–	x	x	x	x	x
Low backache	–	x	–	–	x	x	x	–	–	–
Age at menarche	11	11	13	13	12	11	13	13	13	13
Endometriosis in following organs:	Right ovary, rectovaginal septum	Left tube and ovary, sigmoid, sacrouterine ligament	Left ovary	Left ovary	Left ovary, both tubal corners	Left ovary and tubal corner	Both ovaries sigmoid, cul-de-sac	Right ovary, appendix, cul-de-sac	Tubal stump	Left broad ligament, right ovary
Subsequent operations	–	–	–	–	–	–	–	–	–	–
Blood group	A pos.	A pos.	O pos.	O pos.	O pos.	O pos.	A neg.	A neg.	?	O pos.
Diagnosis made preoperatively	x	x	–	–	–	x	–	x	–	–

4 patients and uterine fibroids in half of the cases. There was widespread endometriosis in all 10 patients. This and the average age of 37 years at the time of operation made radical surgery mandatory in 7 out of 10 patients. Four patients had undergone previous abdominal surgery and there were no recurrences during a follow-up period of from 2 to 6 years.

Review of Published Cases

Goodall's 5 instances of familial endometriosis consisted of a mother and 3 daughters, 3 sisters, and 3 cases of 2 sisters each. All 13 patients had severe and widespread pelvic endometriosis requiring total ablations, and 2 of them were operated upon for an acute abdominal crisis following spontaneous rupture of a large chocolate cyst. Barnes reported one instance occurring in sisters. Both sisters were primigravida, and 3½ months pregnant when operated upon for large chocolate cysts, 5½ and 6 inches in diameter, respectively. In each case the cysts ruptured during separation of the adhesions. Both patients were delivered normally at term. Histological examination showed decidual reaction taking place in an ovarian endometrioma.

Henriksen encountered one case occurring in identical triplets. This case was not published as such, but presented in a discussion at the seventy-sixth annual meeting of the American Gynecological Society in Lake Placid, New York, in June, 1953. All 3 sisters showed a singularly similar pattern of endometriosis. The onset of symptoms, presenting pathology, and type of treatment were identical. They developed severe dysmenorrhea at the age of 16 and required conservative surgery before the age of 25, and total ablations at 28. Gardner's 6 instances occurred in a mother and 2 daughters, 4 sisters, and 4 cases of 2 sisters each. One patient was operated upon for a spontaneous rupture of a chocolate cyst, 2 patients had concomitant carcinoma of the ovary, and 2 other sisters had associated adenoacanthoma of the endometrium. Most of the 15 patients had large chocolate cysts of the ovary, and all had extensive pelvic endometriosis.

Comment

From the above review, consisting of both solitary case reports[8, 9] large hospital series[4, 7] and this series, it appears that in certain cases there is a definite familial tendency toward endometriosis. The occurrence of 5 familial instances (10 patients) in a series of 100 histopathologically proved cases of pelvic endometriosis seems to rule out beyond doubt the law of chance or coincidence. Admittedly, 18 instances are insufficient evidence to prove this point satisfactorily. The fact, however, that in none of the larger series of pelvic endometriosis was any mention of this familial tendency made does not preclude its existence, especially since this factor has not previously been looked for. At the same time there is hesitancy in increasing the already existing confusion by adding a new etiological factor to the 11 previously proposed theories concerning the etiology of endometriosis (transtubal retrograde menstruation theory;[10, 11] direct extension theory[12]; lymphatic[13, 14] and hematogenous[15] spread theory; celomic metaplasia theory[16, 17]; genitoblast theory[18]; dedifferentiation theory[19]; ovarian metaplasia theory[20]; cyclic stimulation theory[21]; mechanical transplantation theory[22, 23]; and composite theory[5]). Special care in taking the family history in future investigations may supply the desired additional data.

Summary and Conclusion

Five instances of pelvic endometriosis occurring in sisters are reported.

Thirteen previously recorded instances are reviewed, bringing the total number to 18.

A familial susceptibility as a predisposing etiological cofactor in endometriosis is postulated.

In establishing the role of this factor further clinical investigation seems to be indicated.

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ENDOMETRIOSIS RESULTING FROM THE TRANSPLANT OF ENDOMETRIUM AT THE TIME OF ACCIDENTAL PERFORATION OF THE UTERUS DURING CURETTAGE

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THE purpose of this paper is twofold: first, to review the current concepts regarding the etiology of endometriosis; second, to present two cases in which we feel that the etiology suggested by the title has rather definitely been established.

The term, endometriosis, as introduced by Sampson, implies the presence of endometrial tissue outside of its normal anatomical location. This concept was further subdivided into a direct type when limited to ectopic foci within the uterus, and indirect when this tissue occurs in extrauterine foci. It is concerning the pathogenesis of the latter, that there seems, even now, to be no unanimity of opinion.

Von Recklinghausen[1] described the disease in 1896, and attributed the origin of such adenomas to growth from the remnants of the Wolffian bodies. Cullen,[2] Russel,[3] and later Blair Bell[4] and Bailey[5] suggested that the disease occurred as the result of growth of Müllerian cell rests. The theory of celomic metaplasia, suggested by Iwanoff,[6] and later championed by Meyer,[7, 8] dominated medical thinking concerning the problem, until the work of Sampson[9-17] which was started in 1921 and continued until his death.

Although the Müllerian theory and the celomic metaplasia theory are usually presented separately, they in general imply an entirely similar process, the former implicating the growth of Müllerian cell rests, and the latter suggesting a metaplastic change of multipotential celomic epithelium to epithelium of the Müllerian type, thought to be brought about by repeated stimulation. The stimulative factor has not been agreed upon as regards spontaneously occurring endometriosis in the human female. Meyer was of the opinion that the factor was an inflammatory one, while Novak,[18] Witherspoon,[19] and, later, Meigs[20] suggested some hormonal disturbance. Sampson proposed the idea that, if the theory were correct, the exciting factor might be the mechanical presence of menstrual blood on the peritoneum.

Meigs,[20] in 1938, advanced the theory that the disease occurred as the result of long uninterrupted hormonal stimulation of embryonic undifferentiated Müllerian cells, and that in patients with hypoplastic Müllerian derivatives, more undifferentiated cells were present and the period of stimulus was shortened. In support of this supposition is the unusually high incidence of the disease in individuals in whom marriage or, more important, pregnancy, occurred relatively late; the age incidence of the disease indicated that many years of menstrual activity preceded the onset of symptoms. He reported clinical internal genital hypoplasia in a significant number of his cases.

In 1921, Sampson initiated the concept of endometriosis resulting from tubal regurgitation of menstrual blood containing viable fragments of endometrial tissue. His theory is in nearly complete accord with the clinical and experimental characteristics of the disease, and he pointed out the following known facts concerning the disease and in support of his theory:

1. That, in the vast majority, the disease was associated with patent tubes, and the occurrence of the disease is rare following early tubal occlusion from gonorrheal salpingitis.
2. That the disease had occurred following operations on the tubes and uterus.
3. That clinical observations of menstrual blood escaping through the tubes into the peritoneal cavity in women operated on at the time of menses were repeatedly reported.
4. That the anatomical location of the extrauterine lesions was most commonly adjacent to the fimbriated ends of the tubes.
5. That the scattering of peritoneal lesions did not conform with the hypothesis of metaplasia occurring under the influence of any stimulative factor.
6. That autologous transplants of endometrium in experimental animals did survive.[23-25]

Sampson, then, became the chief exponent of the theory that endometriosis, wherever found, represented the transference of adult Müllerian tissue to an ectopic site. In reviewing his theory in 1940, he states, "If bits of Müllerian mucosa carried by menstrual blood escaping into the peritoneal cavity are always dead, the implantation theory, as presented by me, also is dead and should be buried and forgotten. If some of these bits are even occasionally alive, the implantation theory is still alive."

In response to the last oft-quoted statement, Te Linde and Scott[27, 28] initiated studies with Rhesus monkeys by operations designed to afford intrapelvic menstruation and were able to produce the disease. The disease was not produced by them after repeated injections of blood onto the pelvic peritoneum, and the assumption was made that the disease resulted from the viability of menstrual epithelium, rather than an irritative celomic metaplasia.

It was later shown by Allen and co-workers[29] that endometriosis of the pelvic peritoneum could be produced in monkeys after completely exteriorizing the cervix from the peritoneal cavity, and he felt that the occurrence of the disease was in some way related to repeated surgical examination with manipulation of the pelvic viscera, rather than to the intrapelvic menstruation.

The last theory of the etiology of this very interesting disease was probably first stated by Halban,[30] and was suggested as a possible mechanism by Sampson in 1925. More recently, Javert[31, 32] has been its chief exponent. It deals with the development of the disease, both direct and indirect, by means of the invasion of the myometrium by endometrium and its secondary spread to extrauterine structures, in the fashion that cancer spreads, either by direct extension, or by blood and lymph borne metastases. Although the theory has not yet received as much publicity as those previously reported, it has much merit and must be adopted to explain the occurrence of endometrial tissue in such areas as the forearm,[33] lung,[34] thigh,[35] kidney,[36] and groin.[37]

It becomes increasingly apparent in any discussion of the etiology of endometriosis that no single theory will suffice to explain every case, and, as repeatedly stated by Novak, all must be assumed to have some importance.

The following two cases, reported from the San Joaquin General Hospital of Stockton, California, stand in direct support of either the theory of Sampson, or the benign metastasis theory of Javert. Though the celomic metaplasia theory seemed to have played no part in these two cases, it is not our purpose to argue against it.

CASE 1.—Mrs. E. C. was a 22-year-old white woman, gravida vii, para vi, whose menstrual activity commenced at the age of 13 years. Periods occurred every 28 days, lasted 5 days, and, though they were associated with the usual menstrual molimina, there was no pain.

On Jan. 10, 1954, she delivered her seventh full-term infant in a rather uneventful fashion. After 48 hours, however, her temperature rose to 102.6° F., and there were associated foul lochia and lower quadrant tenderness. A diagnosis of acute endometritis and parametritis was made and antibiotic therapy instituted with a rapid return to the afebrile and asymptomatic state. She was discharged on the eighth postpartum day.

The patient returned to the clinic after one month, stating that she had been using 6 pads a day since dismissal. Suspecting retained placental fragments, we admitted the patient for dilatation and curettage.

Curettage was productive of about 15 grams of necrotic, fibrotic placental tissue, and during the course of the operation it was felt by the operator that he had inadvertently perforated the uterine fundus. This was clinically confirmed by the development of pelvic peritonitis. The patient returned to an afebrile and asymptomatic state with antibiotic therapy, and was again discharged after 8 days of hospitalization.

The patient then returned to the clinic after 6 weeks, complaining of a constant pain in the left lower quadrant, which had been greatly aggravated by the occurrence of an apparently normal menstrual period 4 weeks after dilatation and curettage. There was, at that time, tender thickening in the adnexa, on the left greater than on the right. Chronic inflammatory disease was suspected, and hot douches and a course of diathermy instituted.

During the next 7 months, the patient visited the clinic regularly, complaining of dysmenorrhea of increasing severity, until she was totally incapacitated three days each month. She also acquired prohibitive dyspareunia and painful defecation. At the end of this time, a 3 by 4 cm. irregular, exquisitely tender mass was palpable in the left adnexa. She re-entered the hospital one year following perforation, and on Feb. 15, 1955, the pelvis was explored through a low midline incision.

The uterus was normal in size, shape, and position. The top of the fundus was densely adherent, on the right, to a loop of transverse colon. There were many black endometrial implants noted throughout the cul-de-sac and on the posterior aspect of the corpus and broad ligament, the largest of which was immediately adjacent to the point of attachment of the transverse colon over an indented scar in the fundus, and measured 5 mm. in diameter. There was a 4 by 5 cm. blood-filled cyst on the left ovary, densely adherent to the sigmoid colon, with obvious gross implants on the latter structure. A 2 by 2 cm. firm, nodular, multiple cystic mass was enclosed between the sheaths of the right broad ligament and overlay the right ureter and hypogastric artery. The right ovary, at its antiligamentous pole, showed two small black implants. A total hysterectomy, bilateral salpingectomy, left oophorectomy, and partial right oophorectomy were accomplished. Conservatism, even to this slight degree, was considered advisable because of the patient's age. She recovered uneventfully and was dismissed on the eighth postoperative day, testosterone, 10 mg. daily by linguets, having been prescribed in view of the remaining ovarian tissue.

Incapacitating symptoms returned within 2 months under testosterone therapy, and surgical castration was advised. The patient was unwilling to undergo further surgery and at present is having the remaining ovarian function suppressed by deep x-ray therapy.

The pathological specimen showed a dense fibrotic reaction in the right cornu, at the site of perforation. A linear scar was present on cross section extending to the serosa and speckled with pepperlike granules which microscopically were typical endometriosis. The nodule overlying the hypogastric artery was also an endometriotic lesion. Recuts from this area failed to prove it to be a lymph node metastasis, although its location suggested

Fig. 1.

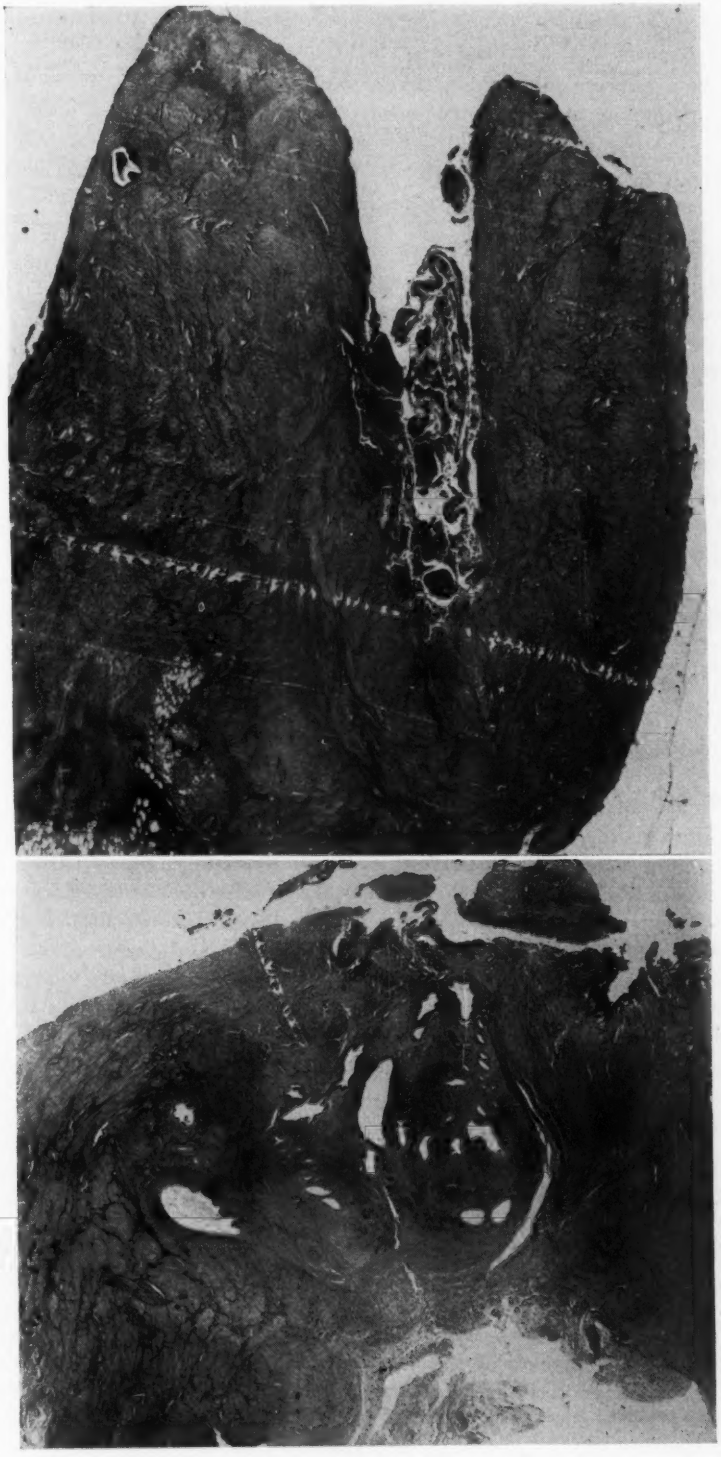

Fig. 2.

Fig. 1.—Case 1. Endometrium in secretory phase lining sinus tract.
Fig. 2.—Case 2. Endometriosis through the entire thickness of the uterine wall.

the possibility. All other areas of gross disease were further confirmed microscopically. There was no gross or microscopic evidence of endometriosis in other sections of the myometrium, unassociated with the area of perforation.

Fig. 1 is a microscopic section taken parallel to the origin of the sinus tract and shows endometrium of the secretory variety lining the sinus tract deep into the right cornu. The fatty tissue in the lower left represents the attachment of the omentum over the site of the perforation. The relatively large glands in the uterine musculature show on higher power a definitely secretory reaction.

CASE 2.—Mrs. T. H. was a 20-year-old white woman, gravida viii. Her menstrual function began at the age of 10 years with periods of irregular occurrence lasting 7 to 14 days associated with mild cramping and the usual menstrual molimina. She had had 4 full-term pregnancies, one of which resulted in a stillborn infant. Four pregnancies ended in early complete abortion, none requiring curettage. The most recent pregnancy ended on Sept. 30, 1954, when she was delivered of a normal full-term infant. She was dismissed after an uneventful postpartum course on the fourth day.

She began bleeding with increased vigor after dismissal, and returned after two weeks on this account. A slightly enlarged, nontender, soft uterus was present on pelvic examination. When oxytocics did not check the blood flow, the patient was admitted 22 days after delivery for curettage.

During curettage, perforation was suspected and clinically substantiated in the immediate postoperative period by the development of lower quadrant pain and tenderness with rebound tenderness present. Antibiotics were administered prophylactically, and the patient never became febrile. The clinical signs subsided and she was discharged after 5 days.

The pathological diagnosis of the surgical specimen was fibromuscular tissue, probably submucous fibroid.

The patient was subsequently followed in the clinic on three occasions, complaining of lower quadrant pain. The only positive pelvic finding was a generalized adnexal tenderness. Two months following the perforation, she experienced resumption of menses and reported to the clinic complaining of painful periods. She was observed through two more periods, at which time she stated she was incapacitated for the first day of each, and described cyclic pain which was reinitiated with menses and persisted with gradual improvement until her next period. She had also acquired dyspareunia, which, although not severe, was a definite and volunteered new complaint. At this time, a 4 by 4 cm. tender mass was palpated in the left adnexa.

Coming in the wake of the first reported case, the striking similarity was noted, and culdoscopy was employed to confirm the clinical suspicion. Typical dimpled, scarred, black endometriotic lesions were viewed through the culdoscope, but the left adnexal mass could not be visualized.

A laparotomy was carried out on Feb. 21, 1955, about 5 months after the perforation, and not quite 6 months after the last full-term delivery.

The uterus was anterior and normal in size, shape, and position. There was an indented scar in the uterine fundus, midway between the cornua. The left ovary was enlarged with a blood-filled cyst 3 by 4 cm. in dimension. There was a 6 mm. implant of endometriosis on the posterior sheath of the left broad ligament. There were two discrete small lesions on the peritoneum of the cul-de-sac and several tiny lesions on the serosa of the sigmoid. The larger lesions were excised, and the ovarian cyst enucleated. The smaller implants were destroyed with electrocautery. A wedge biopsy of the uterine fundus at the site of perforation was accomplished.

The patient recovered uneventfully and was dismissed on the sixth postoperative day. She has since been on 10 mg. of testosterone daily, as linguets, and is symptom free.

The uterine biopsy showed the myometrium at the area of scar to be 8 mm. in thickness. Microscopic blocks taken from the serosal surface, endometrial surface, and midportion of the myometrium all showed uterine glands in the uterine musculature. The other excised lesions were microscopically confirmed as endometriosis. The cyst proved to be a corpus luteum cyst.

Fig. 2 shows the entire section of the uterine wall at the site of perforation. The indentation and scarring of the serosal surface are clearly seen, and remnants of the normal endometrium are visible on the opposing side. The presence of endometriosis penetrating the entire thickness is clearly demonstrated.

One further similar case of endometriosis has been encountered of sufficient severity to warrant partial sigmoid resection, panhysterectomy, and bilateral salpingo-oophorectomy, in a 36-year-old woman whose symptoms brought her to surgery three years after a perforation of the uterus at the time of curettage. This case is not reported in detail because the accident occurred elsewhere, and we have only the history of the patient in this regard.

It is our opinion that these two cases indicate with considerable certainty that the endometriosis encountered was the direct result of the conveying of viable fragments of endometrial tissue through the uterine wall by the perforating instrument, to be implanted on the adjacent extrauterine structures. That this is a logical assumption is borne out by the following facts, common to both of these cases, and uncommon to endometriosis in general:

1. Semi-serial sections through the perforation site in both patients revealed endometrial glands as far out as the serosal surface. In the first case, where the entire uterus was available for study, no other endometriosis was encountered in other areas of the uterus.

2. Both patients presented indisputable proof of uterine perforation at the time of curettage in that neither had had previous surgery or uterine instrumentation, perforation was suspected by the operator at the time of operation, and both were confirmed by subsequent laparotomy.

3. The occurrence of the disease in a 20-year-old gravida viii and a 22-year-old gravida vii is quite contrary to current opinion concerning the spontaneous incidence of disease.

4. Both patients dated the onset of their symptoms to the first menstrual period following the perforating accident.

5. The extent of disease in the first patient was extreme, and it seems exceedingly unlikely that the disease could have antedated her last pregnancy.

6. The gross extrauterine lesions in both cases were in close proximity to the site of perforation.

It is interesting to speculate over the significance of the time interval between delivery and curettage in these two patients. One wonders if at 4 to 6 weeks post partum the hormonal stimulation is such that endometrial tissue is more apt to be implanted than at the time of cesarean section when the spillage is undoubtedly greater. The rarity with which endometriosis occurs under the latter circumstance would seem to indicate that some difference in growth potential of the endometrium exists at these two times.

Summary and Conclusions

1. Two cases of endometriosis folowing perforation of the uterus during curettage within 6 weeks after full-term delivery have been presented in detail. It is concluded that the disease in these two cases resulted from the

direct passage of viable endometrial fragments through the uterine wall on the perforating instrument. Reasons for this conclusion have been given.

2. The theory of celomic metaplasia in these two cases finds no support. The etiology suggested by these two cases supports either the theory of Sampson or the carcinoma-like behavior of endometrium as proposed by Javert.

We wish to express our sincere appreciation to Mr. Howard E. Tribe, University of Utah, Department of Medical Photography, who made the excellent photomicrographs.

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Case Reports, New Instruments and Methods

HILUS-CELL TUMOR OF THE OVARY

Report of a Case

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SINCE tumors derived from the ovarian hilus cells are rare the following case is reported.

H. F., a 50-year-old unmarried white woman, was admitted to the hospital because of hypertension and an excess growth of hair. Twenty-five years previously she had begun to develop an increase in facial and body hair, which gradually became excessive. During the eight years prior to admission she began to lose scalp hair. Her voice gradually changed, became deeper, and more masculine. She also noticed occasional episodes of palpitation and dyspnea. Hypertension was discovered three years prior to admission. This was not severe and was relieved by rest.

Past history disclosed that menses had started at the age of 13 years. Her periods were regular but profuse, generally lasting a week. Nineteen years previously she underwent exploratory laparotomy, and extensive pelvic endometriosis was discovered. This required resection of a portion of small intestine, and an incidental appendectomy was also performed. Two years later she received a course of radium therapy (a total of 12 hours). Her menses then gradually decreased, and finally ceased entirely.

Physical Examination.—The temperature on admission was 98° F.; pulse rate 80; respirations 24; and blood pressure 162/100. She was a slightly obese white woman with a deep, low voice. She complained of fatigue and was noticeably apprehensive. There was marked increase in hair over the face, chest, and back. A typical masculine distribution was noted over the lower abdomen and extremities. The scalp line was receding. The skin was dry and coarse. Slight exophthalmos was noted. The heart and lungs were not remarkable. There was a well-healed lower abdominal scar. The clitoris and labia were enlarged and hypertrophied. Vaginal examination disclosed a small, freely movable cervix. The uterus was small and considered infantile. There was a suggestion of a mass in the left adnexal region.

Laboratory Data.—The blood cholesterol was 368 mg. per 100 ml. Other studies including blood count, urinalysis, and blood chemistry determinations were within normal limits. Roentgenograms of the skull, long bones, pelvis, and chest were unrevealing.

Several days after admission a hysterectomy and bilateral oophorectomy were performed by Dr. W. C. Beck. She did well postoperatively and was discharged within a week.

Pathology.—The uterus was small, being 3.5 by 2.8 by 2.0 cm. in dimensions. There were several subserosal fibromyomas, the largest 5.0 cm. in diameter. Within the endometrial cavity was a benign polyp, 1.2 cm. in length. The right ovary was enlarged, and

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measured 4.8 by 3.5 by 2.5 cm. Near one pole was a poorly defined nodule, 2.0 cm. in diameter (Fig. 1). There was no definite capsule, and the cut surface was gray brown and focally hemorrhagic. The left ovary and tube showed no unusual changes.

Microscopic sections of the right ovary disclosed a tumor composed of broad sheets of uniform polygonal cells. Most of these cells had oval, centrally placed nuclei, and abundant eosinophilic, but slightly granular cytoplasm (Fig. 2). No cytoplasmic inclusions or crystalloids were observed. In some regions the cells were closely associated with small bundles of unmyelinated nerves (Fig. 3). Sections stained with sudan IV disclosed the presence of sudanophilic material within the cytoplasm of these cells.

The initial impression was that this represented a masculinizing ovarian tumor, of perhaps the adrenal-cell-rest type. Representative sections and material from this tumor were submitted to Dr. Emil Novak. Both he[1] and Dr. Robert L. Faulkner agreed that this was a tumor of the hilus or interstitial-cell type.

The patient was examined 8 months after operation. She felt much stronger, and her skin was softer and warm. She thought that there was increased growth of scalp hair, and that the hirsutism of the extremities, trunk, and abdomen was less accentuated.

Fig. 1.—Gross photograph showing the poorly defined hilus-cell tumor of the right ovary.

Comment

The studies of Sternberg[2] have shown that the hilus of the human ovary contains nests of cells morphologically identical with the interstitial or Leydig cells of the testis. These cells are present in at least 80 per cent of adult ovaries. There is a constant relationship of these cells to the nonmyelinated nerves of the hilus. This relationship is also maintained in tumors derived from the hilus cells.

According to Novak[3] a total of 6 tumors derived from the ovarian hilus cells are recorded in the literature. It is difficult to determine the actual number, since differentiation of hyperplasia from tumor has not always been made clear. Typical examples of hilus-cell hyperplasia have been reported by Langley,[4] Taliaferro,[5] Sternberg,[2] and others. Although the latter also have masculinizing signs, bilateral ovarian involvement has occurred in almost all cases. The true hilus-cell tumors, with one exception, have been unilateral. Table I summarizes the cases of hilus-cell tumors reported to date. Approximately half the patients showed some degree of hypertension prior to removal of the tumor.

Clinically and pathologically the hilus-cell tumors should be differentiated from the more common arrhenoblastomas, and the rare "virilizing lipoid-cell

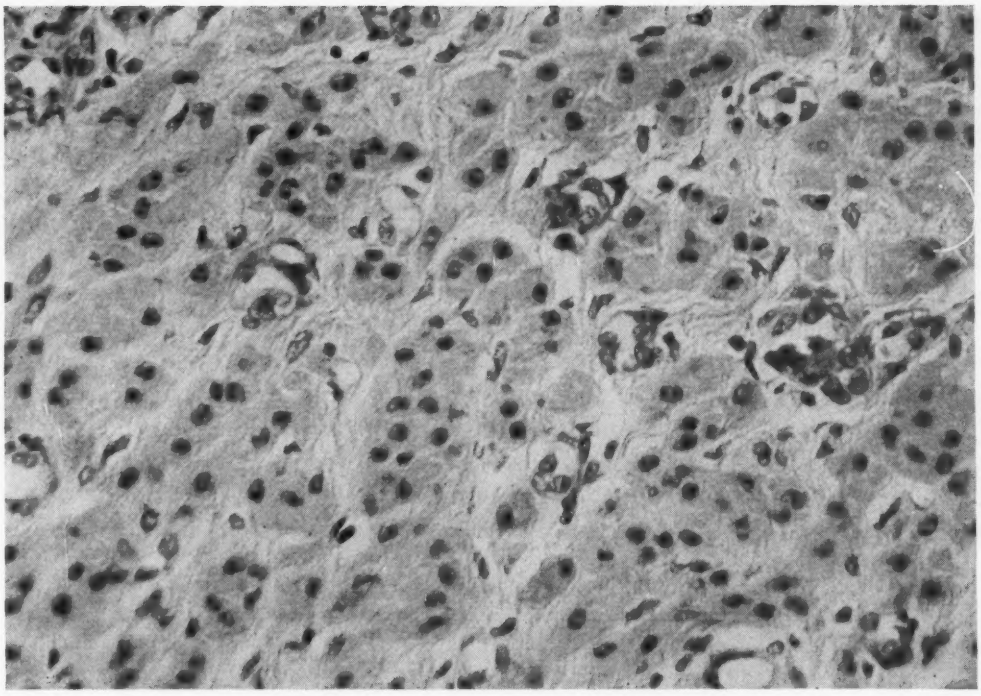

Fig. 2.—Photomicrograph showing the typical large, polygonal hilus cells. (Hematoxylin and eosin; ×360; reduced ⅕.)

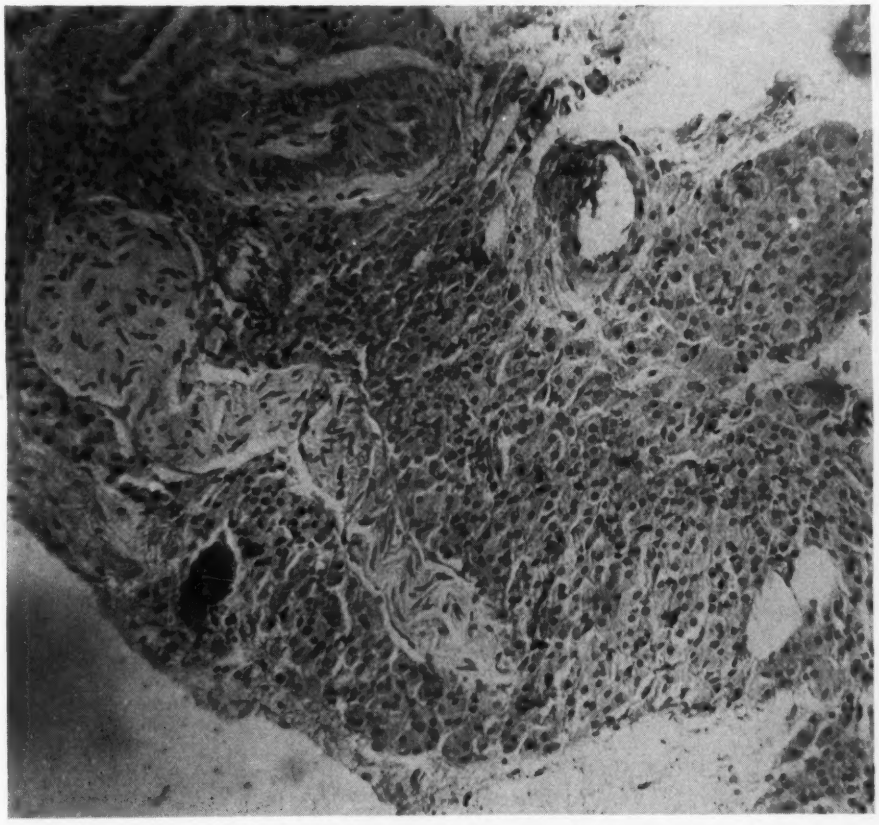

Fig. 3.—The close association of the hilus cells to a nonmyelinated nerve bundle is clearly shown. (Hematoxylin and eosin; ×160).

tumors,'' or adrenal tumors of the ovary. Godsick[10] found 21 tumors of the latter type in the literature up to 1954. The adrenal tumors of the ovary are most common in the 20 to 30 year age group, with only two cases reported occurring after the menopause. Sternberg[2] has shown that the adrenal tumors are yellow, spherical nodules, encapsulated, and usually 1 to 3 mm. in diameter. They duplicate normal adrenal cortex, and have a definite organoid structure.

The arrhenoblastomas include a broad spectrum with a variable pattern, usually with tubular structure and sometimes a sarcoma-like picture, depending upon the degree of differentiation. In a recent publication Langley[4] tends to regard the hilus-cell tumors as a variant of the arrhenoblastomas. The variable structure of the arrhenoblastomas, however, is in direct contrast to the uniform, single cell type of the hilus-cell tumors. A summary of the main features of these three masculinizing ovarian tumors is given in Table II.

TABLE I. SUMMARY OF REPORTED CASES OF OVARIAN HILUS-CELL TUMORS

AUTHOR	AGE OF PATIENT	SIZE OF TUMOR	UNILATERAL	BILATERAL	CRYSTALLOIDS OF REINECKE	ASSOCIATED FINDINGS
Berger[6]	50	0.5 cm.	+		Absent	Persistence of menses
Sternberg[2]	86	1.0, 1.2 cm.		+	+	Hypertension, 17 ketosteroid normal
Sternberg[2]	64	1.0 cm.	+		+	17 ketosteroid normal
Waugh[7]	46	Not stated	+		+	17 ketosteroid increased
Sachs[8]	47	1.8 cm.	+		+	Hypertension, 17 ketosteroid normal. Ectopic adrenal rest (incidental)
Young[9]	27	Not stated	+		Not stated	Pregnancy
Present case	50	2.0 cm.	+		Absent	Hypertension

TABLE II. SUMMARY OF CLINICAL AND PATHOLOGIC FEATURES OF ARRHENOBLASTOMAS, ADRENAL-CELL-REST AND HILUS-CELL TUMORS

TUMOR	AGE GROUP	CELL TYPE	ORGANOID STRUCTURE	CAPSULE	UNILATERAL	BILATERAL	17 KETOSTEROID
Arrhenoblastoma	20-30	Varied	Present	Usually present	+		Normal, or slightly elevated
Adrenal cell rest	20-30	Single cell	Present	Present	+	+	Elevated
Hilus cell	Postmenopausal	Single cell	Absent	Usually absent	+	Rarely	Usually normal

Summary

A case of rare hilus-cell tumor occurring in a 50-year-old woman is recorded. Some of the current concepts with respect to the clinical and pathologic features are briefly discussed.

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MALIGNANT THECOMA

Report of a Case

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MALIGNANT thecomas with metastasis are rare, with only scattered isolated cases reported in the literature.

The following case is interesting because deep roentgen therapy apparently produced temporary remission.

Mrs. N. M., a 67-year-old white woman, was admitted to the hospital complaining of nausea, and cramping lower abdominal pain of several days' duration. Until the onset of her present illness she had been in good health and had suffered no weight loss. Past history disclosed that her menses had ceased at the age of 47 years, and she had had no vaginal bleeding since.

Physical Examination.—The temperature was 98.6° F.; pulse 92; respirations 20; and blood pressure 117/80. The patient was a well-developed elderly white woman in no apparent acute distress. The heart and lungs were not unusual. The lower abdomen was distended and tympanitic. Slight tenderness was noted in the left lower quadrant. Vaginal examination disclosed a large firm mass in the region of the left ovary.

Laboratory Data.—Routine urinalysis, blood counts, and blood chemistry studies were within normal limits.

Hospital Course.—One week after admission an abdominal exploratory operation was performed. A large firm mass was found arising from the left ovary. This was densely adherent to the small intestine and also to the adjacent viscera. It was necessary to resect a segment of ileum before the tumor could be removed. Following operation the abdominal distention was relieved and recovery was uneventful.

Pathology.—The gross specimen consisted of a large firm mass, 17.0 cm. in diameter, which completely replaced the left ovary. The external surface was ragged, nodular, and had numerous fibrous adhesions. Several multiloculated cysts were present within the mass, some of which were filled with blood. The cut surface disclosed numerous gray-white nodules. Other areas were friable and hemorrhagic, with occasional foci of yellow.

Microscopic examination showed a tumor composed of spindle-shaped cells with elongated nuclei. The cytoplasm of the cells was acidophilic, but poorly defined. Occasionally the cells were arranged in parallel rows suggesting palisade formation (Fig. 1). There was abundant hyalinization of the stroma. The most striking finding was the presence of cells with large, bizarre, hyperchromatic nuclei (Fig. 2). Atypical mitoses were fairly frequent. Sections stained with sudan IV demonstrated sparse amounts of sudanophilic material within the cells. Because of the bizarre histologic pattern, the initial impression was that this represented a malignant thecoma of the ovary. Representative sections and material were submitted to the Armed Forces Institute of Pathology.[1] The members of this institution agreed that it was consistent with a malignant thecoma.

Following operation the patient received deep roentgen therapy, with a total of 8,000 r administered to the abdomen and pelvis through several portals. She was then discharged in fairly good physical condition.

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She was readmitted to the hospital 18 months later complaining of abdominal pain and distention. Physical examination disclosed a large mass within the lower abdomen and pelvis. The red cell count at this time was 2.56 million with 8.3 Gm. of hemoglobin per 100 ml. Following preparation with blood transfusions, an exploratory operation was performed. When the abdominal cavity was opened, a large hemorrhagic tumor was found, which completely filled the abdomen and pelvis. This involved the sigmoid colon and most of the small intestine by direct extension. Multiple seedings were noted throughout the visceral and parietal peritoneum. The neoplasm was considered inoperable, but additional biopsies were taken. These revealed a histologic pattern identical to that of the original surgical specimen.

Following operation the patient received routine supportive therapy, but she died within two weeks. Permission for postmortem examination was not granted.

Fig. 1.

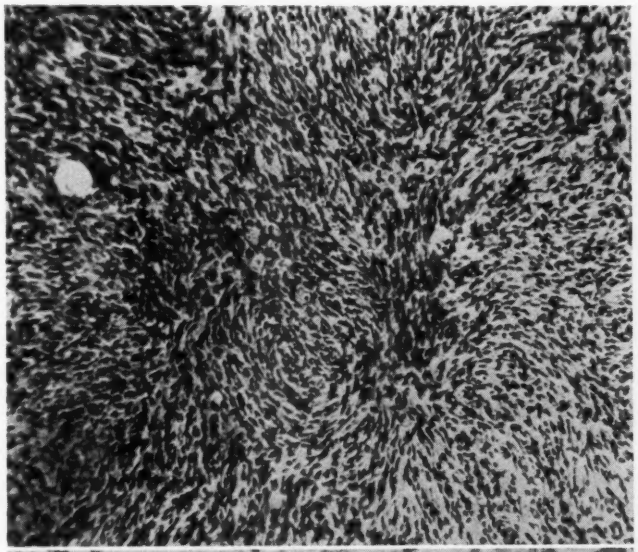

Fig. 2.

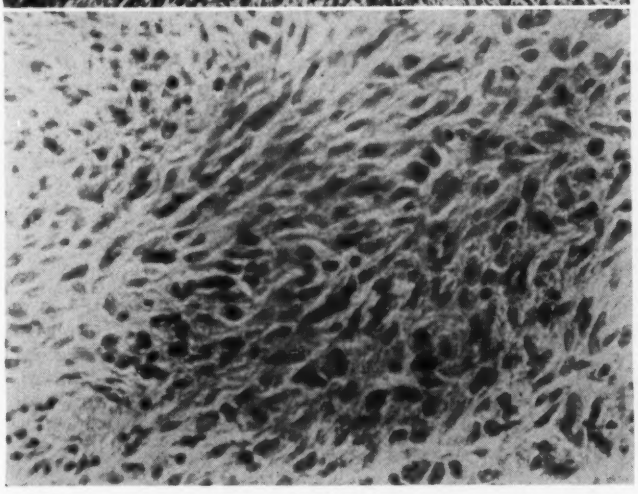

Fig. 1.—Malignant thecoma showing arrangement of spindle-shaped cells resembling palisade formation. (Hematoxylin and eosin; ×160; reduced ⅕.)

Fig. 2.—Photomicrograph showing large, hyperchromatic cells with atypical mitoses. (Hematoxylin and eosin; ×280; reduced ⅕.)

Comment

In a recent survey by Pedowitz and co-workers[2], of 300 cases of thecoma in the literature, only 8 have been definitely malignant. The case presented above fulfills the criteria of malignancy; namely, pleomorphism, hyperchromatism, loss of polarity, and increased and atypical mitoses. The demonstration of local tissue invasion further establishes the malignancy of tumors of this type. In most instances the malignant thecomas have spread to other organs in the peritoneal cavity by direct extension. As yet widespread dissemination, or spread beyond the peritoneal cavity has not been reported. Typical examples with metastases to the left broad ligament have been reported by Rogers and associates.[3] The case recorded by Proctor and others[4] demonstrated diffuse peritoneal spread. One of the most recent cases reported by Jew and Gross[5] exhibited omental metastasis. The latter case was unusual in that it occurred in a 39-year-old woman. Invariably these tumors have occurred in postmenopausal women, and nearly always have been unilateral.

The case reported here is representative of the malignant thecomas. At the initial operation there was local extension to the small intestine. At reexploration, 18 months later, there was additional spread of the tumor to visceral and parietal peritoneum.

The treatment of this neoplasm depends somewhat on the age of the patient and the degree of extension of the tumor. If it is confined to the ovary, adequate wide excision, or unilateral salpingo-oophorectomy appears to be the treatment of choice. In the postmenopausal woman, and particularly if there is spread beyond the ovary, total hysterectomy with bilateral removal of the adnexa is probably indicated. Little information is available concerning the effect of roentgen therapy on this neoplasm. Pedowitz and coworkers[2] thought it to be beneficial, although the curative effect appears to be doubtful. This is borne out by the present case, with fairly heavy dosage being administered to the abdomen and pelvis. Following roentgen therapy this patient survived 18 months, although recurrences eventually caused her death.

Summary

A rare case of malignant thecoma with metastasis is reported. Roentgen therapy was not curative, but did produce temporary remission of the neoplasm.

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THE USE OF ACETONE AS A FIXATIVE IN EXFOLIATIVE CYTOLOGICAL STUDIES*

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ALCOHOL-ETHER fixation for cytological examination has been standard procedure ever since Papanicolaou[1] first described it; it has many advantages. In the first place, transparency is good, making examination of the nucleus possible even in thick smears. Both intra- and extra-cellular proteins are precipitated by the alcohol, while the ether dissolves and extracts the lipids. Finally, slides which have been fixed in alcohol-ether are carried through the polychrome stain of Papanicolaou[1] by being placed first in 80 per cent alcohol, and run down through 70 per cent and 50 per cent alcohol, and to water before the hematoxylin is used.

The alcohol-ether mixture also has some disadvantages. The mixture is highly inflammable, and should not be sent through the mails. Less inflammable mixtures, such as methyl alcohol, isopropyl alcohol, formalin, picric acid, silver nitrate solutions, etc., have been used, but none is as good as alcohol-ether. In 1946, Ayre and Dakin[1] suggested that slides be fixed in alcohol-ether, removed after a proper time, and coated with glycerin before they dried, and then covered with a clean slide. Such preparations may then be mailed. This method prevents drying. Slides fixed in alcohol-ether and then dried are not very suitable for examination, as cells may be distorted, the cytoplasmic-nuclear ratio disturbed, and the staining reaction may be too acidophilic, while the finer nuclear patterns may be obscured. Even when the glycerin method is used, it is not always used correctly. Air bubbles form in the film of glycerin, and the material under these bubbles dries. Glycerin may leak from between the slides, which not infrequently arrive at the laboratory more dry than wet. One more point may be added. Alcohol-ether evaporates with great rapidity, and, in projects involving many slides, the relative expense of using large quantities of these substances is to be considered.

For these reasons, work was begun to see if any other substance could be found which might give as good a result as alcohol-ether as a fixative for cytological material, yet might obviate some of the disadvantages of this mixture. Many organic and inorganic substances were tried, but this paper deals only with the use of acetone.

Absolute acetone is not suitable as a fixative, as it causes too rapid dehydration of the film, parts of which may become detached from the slide. By adding water, the dehydrating avidity of the acetone is decreased, and a nonexplosive

*This study has been supported by a grant from Dr. Charles Crocker.

Fig. 1.

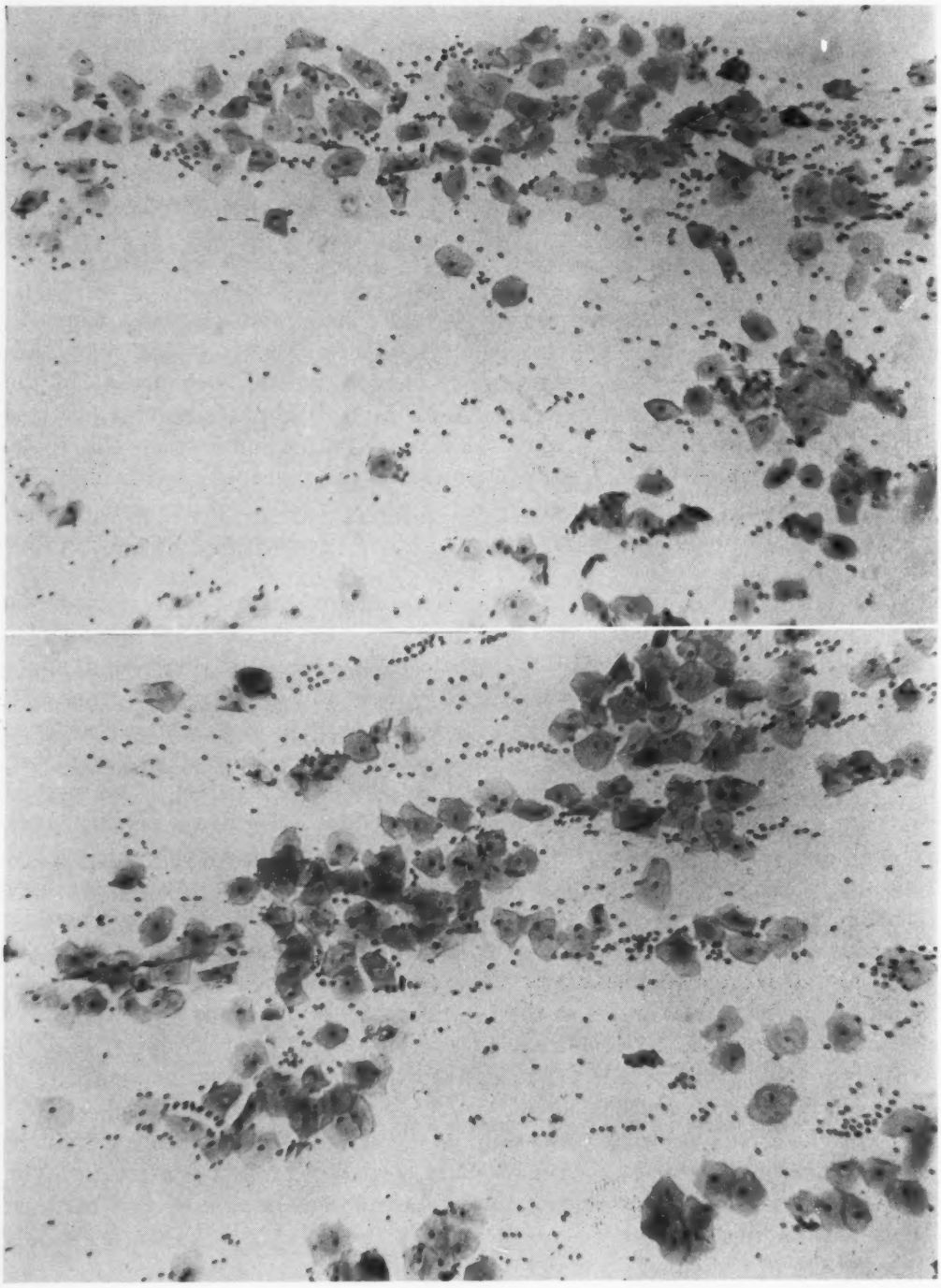

Fig. 2.

Fig. 1.—Vaginal smear fixed in acetone, dried for 96 hours before staining.
Fig. 2.—Same material as in Fig. 1, fixed in alcohol-ether, and stained without drying.

dehydration is achieved. The proper concentration was found to be 90 to 95 per cent. For vaginal, cervical, and intrauterine smears, 90 per cent acetone is used.

The 90 per cent solution is prepared by adding 90 volume parts of acetone N.F. to 10 volume parts of distilled water, and inverting the measuring cylinder several times. This mixture is water clear and has a specific gravity of 0.835 at 20° C. It should be stored in jars the caps of which are not lined with waxed paper, as acetone dissolves paraffin.

Slides are immersed in this acetone solution, and, after 10 to 30 minutes (depending on the thickness of the smear), are removed, and allowed to dry, the acetone evaporating in a short time. They are now ready for transport to the laboratory, and may be mailed or carried by any other method. Many slides are broken during transportation when enclosed in the usual flat cardboard boxes. To avoid breakage, slides should be wrapped in some soft material, and placed in a cylindrical mailing carton, about 1½ inches in diameter and 4 inches in height. Slides so processed may remain dry as long as 2 weeks before staining without becoming unsuitable for examination. Contrary to what happens to smears dried after fixation in alcohol-ether, dried cells after acetone fixation exhibit none of the undesirable changes, such as flattening and distortion of the cytoplasm and nuclei, or loss of affinity for certain stains.

Fig. 1 is a photograph of a vaginal smear fixed in 90 per cent acetone, exposed to air for 96 hours, and then stained. Fig. 2 is a photograph of the same material from the same patient, taken at the same time, fixed in alcohol-ether, and stained without any exposure to air. There seem to be no essential differences between these 2 smears, even under high magnification.

A possible explanation for the preservation of the cells which have been dried after immersion in acetone is that this substance—while dissolving the neutral fats, fatty acids, and a group of other lipids—does not dissolve lecithin and other phospholipids; thus, cells retain a certain resiliency, and maintain their resistance to atmospheric changes. Alcohol-ether fixed cells exhibit artificial morphological changes after drying, as the ether removes the lipids quantitatively, and evaporation takes place at a slower rate, while acetone evaporates from the film almost instantaneously. Acetone-fixed slides should not be run down through decreasing concentrations of alcohol to water. They are put directly into the hematoxylin and processed in the usual way.

Summary

A method for using acetone as a fixative for exfoliative cytological study has been described. This method has the following advantages:

1. The ease of transportation is increased by using dried slides.
2. Fewer steps are necessary in the subsequent staining procedure.
3. Expense is reduced.

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ANTICOAGULANT TREATMENT OF PHLEBOTHROMBOSIS DURING PREGNANCY

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IN THE past three years we have treated three difficult cases of phlebothrombosis during pregnancy. The best treatment is not yet established and any form of management is hazardous to the mother and the fetus. The condition is uncommon, and helpful information based on experience will accumulate slowly. Therefore, it seems worth while to add these cases to those available in the literature.

The use of anticoagulants during pregnancy carries serious risks. Sweet clover disease in cattle[1, 2] and experimental Dicumarol effects in dogs[3] are known to produce hemorrhagic tendencies in newborn calves and pups. Von Syndow[4] in 1947 reported a case in which 1,750 mg. of Dicumarol was administered during the last month of pregnancy. The newborn showed cerebral and subcutaneous hemorrhages. Sachs and Labate[5] in 1949 reported a fetal death in utero in a case where the patient received 3,750 mg. of Dicumarol over a 53 day period. Most reports on the use of anticoagulants have been optimistic, however. Yahr[6] in 1945 safely treated 2 patients in the third and seventh months of pregnancy with about 1,000 mg. of Dicumarol in 7 days. Felder[7] had similar experiences with 2 cases, and Adamson[8] with 4. Weiss,[9] Thornton,[10] and Ware[11] have reported favorable results in 6 cases. Wright[12] successfully treated 9 cases with tromexane. Mansell[13] reported 5 cases in which large amounts of Dicumarol were given, in one of which the prothrombin time was as high as 97 seconds, with no detrimental effect upon the fetus. Ullery[14] summarized the cases in the literature and reported cases treated at Pennsylvania Hospital from 1933 to 1953. Among 135 cases of phlebothrombosis during pregnancy in which no anticoagulant therapy was given, there were 18 pulmonary emboli with 15 deaths. Among 38 patients who received anticoagulants no fatal embolism occurred. Ullery concluded that the condition is best treated with Dicumarol provided meticulous control of the prothrombin level is maintained.

In the following 3 cases* vigorous anticoagulant treatment was given for serious and complicated thromboembolic disease during pregnancy. These cases illustrate the dangerous potentialities of the disease, and the possibility of excellent results with anticoagulants, as well as the possibility of harmful effects.

CASE 1.—A 27-year-old primigravid woman, 16 weeks pregnant, was admitted on May 18, 1952, one week after pain and color changes had appeared in the right calf. Physical examination was normal except for extremely tender, firm, cordlike veins surrounded by

*Cases 2 and 3 were from the private obstetrical service of Dr. Max Tischler.

erythema and swelling overlying the right calf. Homans' sign was positive. The urine, complete blood count, sedimentation rate, prothrombin time, and Lee-White clotting time were normal.

Despite bed rest, elevation of the leg, warm compresses, penicillin and papaverine, tenderness, swelling, and inflammation gradually extended into the thigh. On May 27, temperature and pulse became elevated. On May 29, right pleuritic pain, cough, dyspnea, and bloody sputum suddenly appeared with tachycardia, abdominal distention, and prostration. Chest x-ray showed right costophrenic angle haziness. An electrocardiogram indicated acute cor pulmonale.

The diagnosis was pulmonary embolism secondary to phlebothrombosis, and anticoagulant treatment was begun. A continuous infusion of 5 per cent glucose containing 30,000 units of heparin per liter was adjusted so that the Lee-White coagulation time remained between 30 and 45 minutes from May 29 until June 18 and from June 21 until July 6. Throughout treatment there was no bleeding. The patient remained very ill with chest and leg pain, cough, fever, and tachycardia for about 3 weeks. A large right pleural effusion developed. The thrombophlebitis improved gradually, and on June 18 heparin was discontinued. Within 36 hours severe symptoms recurred in the calf and thigh. The infusion was resumed on June 21 and signs of phlebitis receded, the pleural effusion cleared, and recovery took place. On July 6 heparin was discontinued. She was discharged from the hospital on July 18. The pregnancy progressed normally. On October 24, a healthy baby was born. The postpartum course was normal without anticoagulants. Mother and baby have remained well.

CASE 2.—A 24-year-old woman, 30 weeks pregnant, was admitted on Nov. 1, 1952. Her previous health and first pregnancy were normal. A month previously cough, chest pain, and soreness of the inner aspects of both thighs developed, gradually becoming worse, with increasing pulse rate, low-grade fever, and finally nausea, vomiting, and weakness. Temperature was 100° F., pulse 120, blood pressure 118/76. The physical findings were normal except for obesity and pregnancy. Fetal heart sounds were heard. The hemoglobin was 11 Gm. per 100 c.c., and the leukocyte count was 13,800, with 22 polymorphonuclear leukocytes, 20 band forms, 1 eosinophil, 25 large lymphocytes, 25 small lymphocytes, and 7 monocytes. Urinalysis, serologic test for syphilis, heterophile agglutination, and chest x-ray were normal. Chest pain, nausea, anorexia, vomiting, and low-grade fever continued despite penicillin, streptomycin, pyridoxine, and sedatives. On November 6 urinary output diminished and fetal movement stopped. On November 8, tender, firm swelling of the saphenous veins from the knees to the femoral canals was first noted. Vomiting of large amounts of dark brown fluid and diarrhea developed. The patient appeared critically ill, confused, dehydrated, febrile, with pulse 130, blood pressure 80/20. The fundi were normal. The mouth was parched and covered with sordes. Respirations were rapid, but the chest was clear. Fetal heart sounds could not be heard. There were indurated, tender longitudinal cords in the inner aspects of both thighs, and 3 plus edema of the thighs and legs. The hemoglobin was 12.5 Gm. per 100 c.c., leukocytes 18,250 with 20 polymorphonuclear leukocytes, 39 band forms, 40 lymphocytes, 1 monocyte, and 6 nucleated red cells per hundred white cells. Urinalysis showed specific gravity 1010, albumin 1 plus, 15 leukocytes and 12 hyaline casts per high-power field. An electrocardiogram was normal. On November 9 there was complete anuria for 24 hours. The blood urea nitrogen was 109.

The diagnosis was not clear. It was thought that gradually progressive phlebothrombosis of both saphenous veins, with small pulmonary emboli, had simulated bronchitis. Nausea and vomiting led to dehydration, increase in the phlebothrombosis, hypotension, oliguria, and finally anuria and uremia. A transfusion was given and the patient was placed in an oxygen tent. Intravenous fluids were started, with 10,000 units of heparin injected into the tubing every 3 hours. Combiotic and lipo-adrenal extract were given daily. She remained in critical condition for 2 days with increasing somnolence, confusion, cyanosis, and hypotension, but urinary output returned. By November 11 she could take fluids without vomiting. The intermittent heparin was changed to a continuous infusion containing 30,000 units of heparin per liter, keeping the Lee-White coagulation time between 25 and 40 minutes.

On November 12 the blood urea nitrogen was 107 mg., leukocyte count 44,000, hemoglobin 12 Gm. per 100 c.c., chlorides 540 mg. per cent, carbon dioxide combining power 35 per cent. Blood culture showed no growth. On November 13, a macerated fetus was delivered. Heparin was discontinued during labor, which was uncomplicated except for hypotension. Following delivery the course was stormy but slowly favorable. Hypotension improved with intravenous mephentermine sulfate. The blood urea nitrogen decreased rapidly to normal. A large abscess which formed under the scar of an old excised pilonidal sinus was drained and healed gradually. Improvement in the phlebothrombosis was slow. Persistently low prothrombin led to finding serum albumin 2.7 Gm., globulin 3.5 Gm., cephalin flocculation 4 plus. Dicumarol was withheld because of this evidence of liver damage. The leukocytosis subsided and nucleated red cells disappeared from the peripheral blood. On November 27, the patient suddenly had a large hematemesis. The heparin was discontinued and bleeding promptly stopped. Improvement thereafter was satisfactory. She was discharged on December 9, and has remained well, but intermittent swelling of both legs, and evidence of permanent liver damage have persisted.

CASE 3.—A 43-year-old primigravid woman, 16 weeks pregnant, was admitted on Dec. 11, 1954, thirty-six hours after the onset of pain and swelling of the right leg. Thigh and leg were swollen to about twice normal size. There was tenderness along the saphenous vein in the thigh, with redness and extreme tenderness overlying Hunter's canal. The temperature was normal. The hemoglobin was 9 Gm. per 100 c.c. and the leukocyte count was 8,600 with normal differential. Urinalysis, Lee-White coagulation time, and prothrombin time were normal. The diagnosis was phlebothrombosis and thrombophlebitis of the right saphenous and iliac veins.

A continual infusion containing 30,000 units of heparin per liter was started, and the Lee-White clotting time kept between 30 and 50 minutes from December 11 until December 17. Improvement was rapid. By December 14 the swelling was gone and there was only slight tenderness at the femoral canal. Dicumarol was started on Dec. 15 and heparin stopped on Dec. 17. A total of 1,275 mg. of Dicumarol was given in 11 days. During the last 5 days a prothrombin time of about 33 seconds (control 16.5) was maintained with 75 mg. daily. The patient was discharged on December 24 to continue this dosage at home. This was stopped on December 27 when home prothrombin determinations were found unreliable.

On January 3 discomfort returned in the right leg and next morning she was readmitted to the hospital with recurrent pain and severe swelling, tenderness of the calf and inner aspect of the thigh, and positive Homans' sign. Intravenous heparin was resumed, and the coagulation time was maintained at about 30 minutes from January 4 to 6. Dicumarol was started on January 4. Satisfactory (30 to 35 seconds) prothrombin times were obtained with more difficulty than formerly, and from January 4 to 15 she received a total of 1,675 mg. of Dicumarol. The required daily dose seemed to be 150 mg. Progressive improvement took place, fetal movements were normal, and she was discharged on January 15 feeling well. Dicumarol, 100 mg. daily, was continued from January 17 to 20 with prothrombin determinations done at the hospital laboratory. The prothrombin times of January 17, 19, and 21 were 35, 38, and 57 seconds; therefore Dicumarol was withheld for 3 days. At about this time fetal movements stopped. On January 24 the time had decreased to 37 seconds and Dicumarol was resumed with a dosage of 75 mg. daily. There was no bleeding, and she remained well. The prothrombin time varied erratically between 23 and 40 seconds on the reduced dosage. On March 27 a macerated fetus was delivered. Fetus and placenta showed no evidence of hemorrhage. Following delivery Dicumarol was continued for 2 weeks. The patient made a complete recovery and has remained well.

Comment

The disastrous possibilities of phlebothrombosis during pregnancy and the risk in delayed adequate treatment are illustrated in Cases 1 and 2. The common complaint of leg pain in pregnancy, the infrequency of the condition,

and the possibility of its developing as an obscure complication of an intercurrent infection or with constitutional or embolic manifestations can readily delay diagnosis. In Case 1 anticoagulant therapy was lifesaving for the mother with safety to the fetus. On the other hand, in Case 3, where anticoagulants were essential to control severe and recurrent phlebothrombosis, there is reason to believe that Dicumarol played a part in the loss of the fetus. Carefully graded doses, constant observation, and dependable prothrombin determinations failed to prevent a brief excessive prothrombin fall which coincided with fetal death.

These cases bring to 40 the total reported number treated with anticoagulants during pregnancy. Fetal loss associated with Dicumarol has occurred in 3. Withholding anticoagulants, however, does not eliminate this danger; in Case 2 death of the fetus occurred as a result of complications of phlebothrombosis before anticoagulants were started. This experience is far too meager to permit even tentative conclusions, yet our impression is that heparin offers a safer means of control than Dicumarol. The expense and cumbersome procedure required by heparin are anything but satisfactory, but loss of the fetus in Case 3 and the gratifying result in Case 1 suggest that, despite the hardships, heparin is to be preferred.

Summary

Three cases of phlebothrombosis during pregnancy have been described. The first, complicated by a severe pulmonary embolus, was treated with heparin, with full recovery of the mother, and birth of a normal baby. The second, complicated by probable pulmonary emboli, dehydration, anuria, and uremia, resulted in fetal death before anticoagulants were given. The third patient recovered from phlebothrombosis with heparin and Dicumarol but death of the fetus occurred while she was under treatment. There is reason to believe that Dicumarol played a part in the fetal death.

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THE TREATMENT OF HYPEREMESIS GRAVIDARUM WITH HYPNOTHERAPY

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NAUSEA and vomiting occur in about half of all pregnancies, but fortunately pernicious vomiting is much less frequent. Most observers feel that there is a strong psychogenic basis for all cases of hyperemesis gravidarum, and that current therapy is therefore inadequate. Among the various treatments that have been recommended are the following: ACTH, vitamins B_1, B_6, C, and K, glucose and insulin, estrogens, progesterone, testosterone, antihistamines, Dramamine, Thorazine, procaine infiltration of the lower cervical sympathetic cord, intestinal adsorbents, injections of husband's blood, nitrites by inhalation, duodenal tube feedings, etc.

In view of the urgency of some situations and the dangers of dehydration and acute yellow atrophy, however, and recognizing that psychotherapeutic techniques offered the best chance of success, Angalo[11] in 1942 reported a case of hyperemesis gravidarum cured by hypnosis. This patient, a young gravida iv, para 0, had had three previous pregnancies, in each of which uncontrollable vomiting had developed, and in each of which abortion was necessary. In 1946, Kroger and DeLee[12] reported a series of 19 cases completely relieved by hypnosis. They reasoned that, since many of these patients have emotional conflicts which are repressed, hypnosis should be efficacious, either by eliciting the underlying psychogenic factors (hypnoanalysis) or by raising the vomiting threshold. In spite of the remarkable results with hypnotherapy, a search of the literature shows that very few cases have been reported. It is the purpose of this article to bring this method of therapy to the attention of other obstetricians in order to decrease the number of therapeutic abortions. We would greatly welcome reports from other sources.

Methods and Material

Since 1950 our most intractable cases of hyperemesis gravidarum have been chosen for special study and hypnosis. Inasmuch as exact criteria could not be stated, our clinical experience was the sole factor in determining severity. Twelve cases have thus been collected.

Well over 90 per cent of normal women are susceptible to hypnosis, a state of extreme hypersuggestibility used for removal of symptoms. After the establishment of rapport (dependence of the patient on the physician), the hypnotic trance is easy to induce. The actual technique we used was that of Dr. Lewis R. Wolberg.[9] Suggestions are made with regard to vomiting. Posthypnotic suggestions, which last for about a month, are separate hypnotic states arising spontaneously after the somnambulistic state. In cases where

TABLE I. SUMMARY OF COURSE OF TWELVE PATIENTS WITH HYPEREMESIS GRAVIDARUM TREATED BY HYPNOSIS

PATIENT	AGE	GRA-VIDITY	PARITY	PERIOD OF GES-TATION	NO. OF DAYS OF SEVERE VOMITING PRIOR TO INITIATION OF HYPNO-THERAPY	ACETONURIA PRIOR TO HYPNO-THERAPY	EMOTIONAL PROBLEM	NO. OF SESSIONS OF HYPNOSIS FOR IMMEDIATE RELIEF OF VOMITING	ADDITIONAL MONTHLY SESSIONS OF HYPNOSIS	RESULT OF PREGNANCY	PREVIOUS OBSTETRICAL COMPLICATIONS
F. G.	31	iii	ii	8 weeks	8	4+	Homesick-ness	1	2	Full-term living female	Hyperemesis gravidarum
A. R.	22	ii	i	10 weeks	2	2+	Domina-tion by in-laws	1	1	Full-term living male	None
L. C.	25	iii	i	6 weeks	4	2+	Financial	2	0	Spontaneous abortion at 12 weeks	Spontaneous abor-tion at 8 weeks (first pregnancy)
C. M.	21	ii	i	11 weeks	6	0	Inadequate housing	1	0	Full-term living female	None
R. W.	29	i	0	5 weeks	3	1+	Loss of career	2	1	Full-term living female	—
H. G.	31	iii	i	7 weeks	4	4+	Impending divorce	3	1	Full-term living male	Spontaneous abor-tion at 10 weeks (first pregnancy)
A. S.	20	i	0	6 weeks	1	3+	Inability to adjust to pregnancy	1	2	Full-term living female	—
M. B.	19	i	0	6 weeks	4	0	Aversion to pregnancy	1	1	Full-term living male	—
F. K.	25	ii	i	8 weeks	6	0	Inadequate housing	1	0	Full-term living female	Midforceps
R. Q.	32	iv	iii	10 weeks	10	2+	Didn't want another child	1	0	Full-term living male	Long labor, per-sistent posterior position
B. S.	34	iii	ii	12 weeks	4	2+	Fear of pregnancy	1	1	Full-term living female	Cesarean section for placenta previa
J. D.	24	ii	i	10 weeks	3	3+	Inadequate housing	1	3	Full-term living female	None

hypnoanalysis is preferred, the key to the treatment is the ability of the somnambulist to remember distant events. According to Kroger and DeLee, any physician can learn to use hypnotherapy.

Case Report

F. G., a homesick war bride, aged 31, gravida iii, para ii, whose last menstrual period was May 8, 1950, was admitted to Lutheran Hospital on July 23, 1950, with the chief complaint of daily nausea and vomiting since July 17. She had had the same condition in both of her previous pregnancies, and required eleven days of hospitalization in the first trimester of her last pregnancy. They both resulted in normal, full-term deliveries, however. Her menstrual history was not remarkable. Past and family history were negative.

Examination showed a dehydrated, well-developed 31-year-old white woman, retching uncontrollably. There was no positive neurologic sign. The lungs were clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. The liver and spleen were not palpable. The abdomen was soft, and the fundus of the uterus was barely palpable over the symphysis. The temperature ranged from 98 to 99.8° F. during her entire stay in the hospital.

Laboratory results on July 24 were as follows: Urine: faint trace of albumin, 1 plus glucose, 2 to 4 white blood cells, rare red blood cell, 4 plus acetone, many epithelial cells. Blood count: hemoglobin 80 per cent, red blood cells 4.00 million, white blood cells 9,700, polymorphonuclear leukocytes 77, lymphocytes 14, eosinophils 3. Blood group: O, Rh positive. Blood cholesterol 150 mg., creatinine 1.2 mg., nonprotein nitrogen 25 mg., glucose 110 mg., and chlorides 320 mg. per 100 c.c.

Treatment consisted of intravenous fluids (5 per cent amino acids in 5 per cent glucose, 2,000 c.c., and 5 per cent glucose in isotonic saline, 1,000 c.c. daily), 100 mg. vitamin B_6 intramuscularly daily, barbiturates by injection, vitamins by injection, and almost complete isolation. The vomiting continued for two more days on this regimen. Strong consideration was given to the possibility of therapeutic abortion, because of the rapid deterioration of her condition. In desperation, hypnosis was tried. Induction was easy, and she was kept in this state for a full hour. She was able to retain some food that same day, but we thought it advisable to repeat the hypnotherapy on July 26 and 27. Intravenous fluids were not used after the first hypnotic session. She was discharged from the hospital on July 31 in excellent condition. On August 28 and September 27 she was again hypnotized, not because of a return of the vomiting, but as a prophylactic measure. She was delivered on Feb. 12, 1951, of a full-term female from left occipitoanterior position by low forceps. She is at this date in the best of health.

Results

Table I summarizes the history, treatment, and results in all 12 cases in the series. While the number of cases is small, it is encouraging to note that all 12 patients benefited from this therapy. All the mothers recovered, and have been followed up to this date. All of the pregnancies resulted in normal babies, except that of L. C., who had a spontaneous abortion at 12 weeks. She had also had a previous spontaneous abortion.

Summary

Twelve cases of hyperemesis successfully treated with hypnosis are presented in order to stimulate further utilization of this therapy. The methods are simple and can be mastered by any physician.

We wish to express our gratitude to Dr. William J. Kurz, Dr. Hildegard Bierdemann, and Dr. Leonard Cibley for their great assistance in this study.

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HYDATIDIFORM MOLE IN A 12-YEAR-OLD GIRL

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HYDATIDIFORM mole can occur at any age at which pregnancy is possible. It has been noted, however, that the frequency of its occurrence after the age of 35 is rather high for the relatively small number of births after this period.[1] At least 9 cases of mole in women past 50 have been reported[2-10] and the incidence here also seems considerably greater than the usual figure of one mole to every 2,500 normal pregnancies.[11]

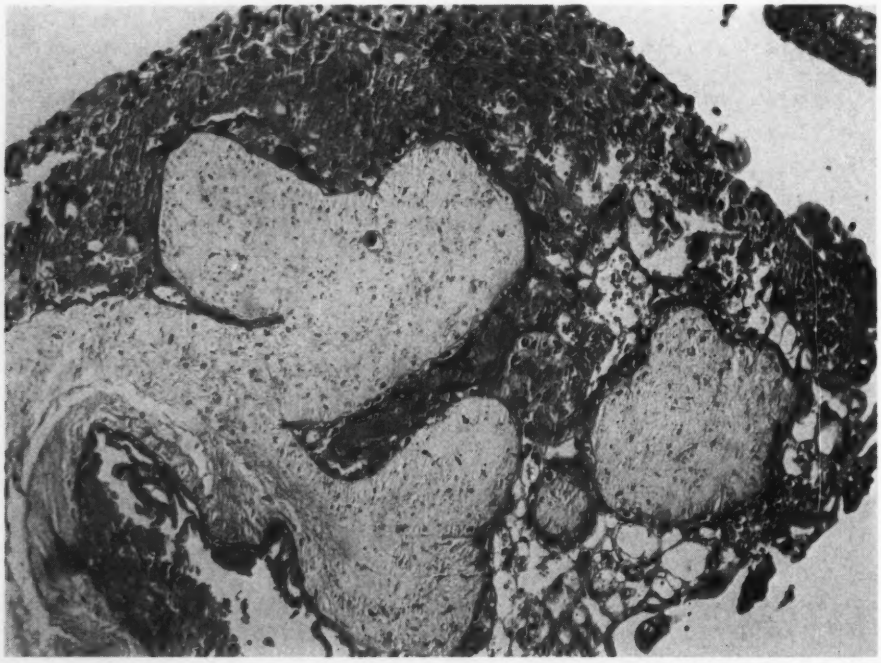

Fig. 1.—Vesicular tissue removed from the cervical canal showing the characteristic features of a mole: (1) edema of the stroma; (2) absence of blood vessels; (3) trophoblastic proliferation. (×130; reduced ¼.)

Cases of pregnancy in 5½-, 6-, and 7-year-old girls have been reported[12, 13, 14] and pregnancy in girls of 12 to 15 is not infrequent. Certainly, pregnancy is more common in the 12 to 15 year group than in women over 50, and yet moles in the former group are quite rare. The literature on this subject is very scanty. Das,[15] in 1893, reported a case of mole in a 13-year-old Indian girl, and Hristu[16] reported a case in a 14-year-old girl in 1933. These are the only cases occurring in very young girls that we have been able to find.

Actually, as Mathieu[17] stated, "The incidence and age incidence are only of didactic importance. . . . The important factor is that any patient in the childbearing age might harbor a mole and therefore one must constantly have this condition in mind."

We are herewith presenting a case of mole in a 12-year-old girl. Besides carefully searching the literature, we have also communicated with those who have had much experience with moles,[18, 19, 20] and this appears to be the youngest such patient so far encountered.

G. S., No. 16540, a 12-year-old Negro girl, was admitted to the hospital on Oct. 6, 1954, because of profuse vaginal bleeding for one day. She stated that she had had a normal menstrual period the early part of September, and admitted to intercourse only in August.

Menses had started at the age of 9, occurred every 28 days, and lasted for 5 to 6 days. There were no previous menstrual disturbances or history of previous pregnancy.

The patient appeared older than her stated age; she was 5 feet, 8½ inches tall and weighed 130 pounds. Her age was verified by other records, however. Physical examination revealed a soft uterus, 8 to 10 weeks in size, with an open cervix. A mass of spongy tissue consisting of clusters of tiny vesicles and measuring 5 by 10 cm. was removed from the cervical canal.

An Aschheim-Zondek test on urine obtained the following day was positive. A curettage was performed and the vaginal bleeding stopped. A chest x-ray was negative and another Aschheim-Zondek test done on Oct. 18, 1954, was negative. The patient was discharged on October 20. Unfortunately, she failed to return to the Follow-up Clinic for further studies.

Pathologic examination of the tissue removed from the cervix at the time of admission showed the typical picture of a hydatidiform mole (Fig. 1). The curettings obtained the following day showed only decidual endometritis with no residual molar tissue.

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CERVICAL PREGNANCY*

Case Report

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PRIOR to 1911, when Rubin[1] reported 3 proved cases, the existence of cervical pregnancy was viewed with great skepticism. At that time, Rubin also enunciated the following criteria which must be fulfilled before a diagnosis of cervical pregnancy could be established:

1. There must be cervical glands opposite the placental attachment.
2. The attachment of the placenta to the cervix must be intimate.
3. The whole, or a portion of the placenta must be below either the entrance of the uterine vessels or the level of the internal os.
4. Fetal elements must not be present in the uterine cavity.

Studdiford,[2] reviewing 28 previously reported cases and adding 2 of his own in 1944, postulated that implantation and growth of the fertilized ovum in the cervical canal are caused by an arrest of the progressive development of the blastodermic vesicle. Such an ovum, he theorized, does not attain the maturity required for imbedding until it has dropped through the uterine cavity and reached the cervical canal.

To date, there has been a total of 46 reported cases of cervical pregnancy, the latest by Cummin[3] in 1955. It is interesting to note among these patients the high incidence of spontaneous abortion. As a matter of pure speculation, could there be an element of an incompetent internal os as a predisposing factor?

The symptomatology of the previously reported cases presents a rather constant pattern. Vaginal bleeding, as a result of necrotic changes in the cervical mucosa which functions as a decidua capsularis, occurs early and may even imitate the periodic pattern of a normal menstrual cycle. This seeming absence of amenorrhea is misleading in making the diagnosis. Studdiford[2] believes that rupture of the thinned-out cervix accounts for sudden profuse hemorrhage. This also leads to formation of hematomas at the base of the broad ligament or beneath the bladder, which give rise to the other frequently noted symptoms of vague abdominal discomfort and dysuria.

The case we are presenting is supported by clinical and pathological evidence. It differs from the average in that this patient carried her cervical pregnancy for five months, whereas the usual length of such gestation is three months. There is no case on record of a cervical pregnancy going to term.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Nov. 3, 1955.

In adding this case to those already reported, we wish to emphasize the importance of early diagnosis. It is the only effective means of avoiding an obstetric catastrophe in this condition, which carries a maternal mortality of 20 per cent.[2]

Mrs. A. D., a 36-year-old white para i, was first seen in the receiving ward of the Pennsylvania Hospital on Sept. 18, 1955, at 10:00 P.M., complaining of vaginal bleeding of a week's duration that had suddenly increased in quantity. The past medical history was not revealing except for an appendectomy in 1953. The patient had her last menstrual period on April 22 and it was normal in every respect. Since that time, she had experienced premonitory signs of pregnancy, including morning nausea, breast enlargement and tenderness. In addition, there had been intermittent spotting during the past 3 months.

Examination showed an extremely obese white woman in obvious distress. The oral temperature was 99° F., pulse 90, blood pressure 100/70, and hemoglobin 11 Gm. The head, neck, and chest findings were all normal. The obese abdomen was moderately tender in both lower quadrants. The uterine fundus could not be outlined definitely. The vagina was filled with several large blood clots. After these were evacuated, speculum examination showed the unusually large cervix to be bluish and widely dilated, with tissue protruding from the external os.

The patient was immediately admitted with a tentative diagnosis of placenta previa and premature labor at 5 months' gestation. Her blood was typed and cross-matched and she was taken to the operating room for further vaginal examination after an intravenous infusion of Pitocin solution was started. Re-examination, with the patient under general anesthesia, showed the bleeding to have increased considerably. The cervix was judged to be 7 cm. dilated and placental tissue was protruding. Because of the bleeding, it was decided to remove the placenta manually. A living, markedly immature male fetus, 10½ inches long and weighing 9½ ounces, was also delivered with the placenta. This fetus lived approximately 3 hours.

Immediately following the delivery, there was a profuse hemorrhage which could not be controlled by intravenous Pitocin, intravenous ergonovine, and massage of what was then thought to be the uterine fundus. The patient went rapidly into shock. A blood transfusion was started and the case re-evaluated. At this time examination disclosed an enormous cervix which was completely dilated. The cervical canal was shaggy in appearance and had several pieces of placental tissue still attached to it. Bleeding was very brisk from the entire surface of the canal. The uterine fundus was then palpated as being firm and but slightly enlarged. It was at this time that the diagnosis of cervical pregnancy was made.

The hemorrhage was controlled by tight cervical and vaginal packing. The patient, having received 2,500 c.c. of whole blood and 2,000 c.c. of dextrose in water, gradually responded and the vital signs returned to normal. Two days later, when the packing was removed, the cervix showed definite evidence of involution and a biopsy was taken. No further bleeding occurred and the patient was discharged from the hospital. When seen 2 weeks later in the outpatient department, she had no complaints; the cervix was observed to have returned to normal except for the presence of a large erosion.

The gross pathologic description of the placenta was of a specimen weighing 70 grams and measuring approximately 8 cm. in diameter. Its maternal surface was unusually shaggy, and some of its cotyledons were attached to the membranes by only a few fibrous tags. The cotyledons themselves were friable and varied in color from pinkish gray to purple red. The fetal surface showed the normal appearance. The cord measured 16 cm. in length, being attached centrally. The completeness of the placenta could not be ascertained.

The microscopic examination of the placenta showed that the chorionic villi were relatively large and the fetal vessels small. The villi were surfaced by a distinct trophoblastic layer which was, at some points, double. The syncytial nuclei were often aggregated into small knots. There was a neutrocytic infiltration in the amnion, as well as some fibrin deposition.

The pathologic diagnosis was immature placental tissue and acute chorioamnionitis.

The gross pathologic description of the cervical biopsy showed the specimens to be irregularly shaped fragments of soft, grayish-tan tissue which were motled purplish red.

Under microscopic examination, the biopsy specimens were recognized as cervical tissue by the presence of a fibrous stroma and the occurrence of mucous gland spaces lined by columnar cells with basal nuclei and clear cytoplasm. A portion of the specimen had undergone a transformation in which the stroma was converted into polygonal eosinophilic decidual cells, into the area of which there had been neutrophilic infiltration and extravasation of red blood cells. The stroma was also infiltrated by cells of a different type. These had a basophilic cytoplasm and relatively large nuclei which were hyperchromatic and occasionally multinucleated. The last represented invasive trophoblastic elements.

The pathologic diagnosis was fragments of cervix with decidual reaction and trophoblastic invasion (Fig. 1).

Summary

A case of cervical pregnancy meeting the four criteria of Rubin has been reported. Hemorrhage, caused by removal of the placenta which had been intimately attached to the cervix, was fortunately controlled by prompt packing.

This case emphasizes the urgent necessity of early diagnosis in order to apply vigorous measures to avert the potential disaster attendant upon cervical pregnancy.

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THE "MEMBRANE MITT." A GAUZE MITT FOR REMOVAL OF RETAINED SECUNDINES

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THE postpartum uterus may be entered with comparative safety.[3] In fact, some authors advocate routine manual exploration.[2]

When retained secundines or fragments of placenta are still present in the uterus, postpartum bleeding continues. It is the custom of obstetricians to remove these either with the gloved hand alone or aided by a piece of gauze.[1] Since the gloved hand is very slippery, many prefer to cover it with gauze.

The disadvantages of free gauze are two: (1) It may slip off the glove and (2) it does not permit free play of the fingers.

Fig. 1.—The "membrane mitt" showing open ends allowing free play of the fingers.

Because of this we have devised a simple, inexpensive mitt of gauze which we call the "membrane mitt." This does not require technical skill to make or use.

Material: (1) gauze with a selvage on one side or both sides; (2) umbilical tape. The gauze is cut 20 inches long and 18 inches wide, two layers thick. If a selvage is on one side only the other side is folded to within one-half inch of the selvage. This is to avoid loose threads. If there is a selvage on both sides, the gauze is folded selvage to selvage. The gauze is then folded in half, end to end to make a mitt, each surface of which is four layers thick. The side edges are left open. A slit is made through all the eight layers in one corner of the open ends. A piece of umbilical tape twelve inches long is introduced through this slit and is tied firmly at one end, leaving the other end free. A similar slit is made in the other free corner and a similar piece of umbilical tape is tied in the same fashion.

The mitts are packaged in lots of two and sterilized like any other surgical dressing.

To use, one merely slips the sterile gloved hand into the sterile mitt. The umbilical tape is tied about the wrist by a sterile assistant. If no sterile assistant is available a sterile rubber band may be slipped over the wrist by the operator himself. (Fig. 1.)

After being fastened to the wrist, the mitt is lubricated well with liquid green soap or similar lubricant and the hand inserted into the uterus with the fingers cone shaped in the usual manner.

Although a first glance at the "membrane mitt" may make it appear bulky or awkward, actual use will show it gives free play to fingers and wrist. It does not take up more room than gauze and does not impair the tactile sense.

At the Harlem Hospital we have found the "membrane mitt" a convenient aid in removing retained secundines and fragments of placenta from the postpartum uterus.

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Reviews and Abstracts

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Review of New Books

Obstetric Practice. By H. Speert, and A. F. Guttmacher. 478 pages. New York, 1956, Landsberger Medical Books, Inc. $7.00.

Intended for the general practitioner, this book presents the most recent information available in the field of obstetrics in an intelligible and concise fashion with controversial concepts kept at a minimum. The diagnosis and management of clinical problems are handled in a practical manner, and the correlation of medicine and surgery with the problems of obstetrical therapeutics is stressed clearly.

However, the all-encompassing nature of the book is a weakness: too much is covered at too superficial a depth. The omission of chapters on anatomy and physiology of the reproductive organs, placentation, and fetal development, because of the reader's assumed familiarity with basic techniques, is not justified. These should have been included if only for the sake of review.

The second author of this text is one of the most able writers of scientific English in America. Unfortunately, his usual sparkling prose is for the most part missing from this writing.

Blakiston's New Gould Medical Dictionary. Edited by N. L. Hoerr and A. Osol. Second edition. 1463 pages with 252 illustrations. New York, 1956, Blakiston Division, McGraw-Hill Book Co., Inc. $11.50.

This second edition adds thousands of new words to those included in the first. Not only have new medical words been added, but also terms from allied fields such as chemistry, physics, biology, and pharmacology.

In the alphabetic listing there appear trade names of drugs and many biographic notes. The etymology is given for most words, with the Greek roots Anglicized. As a guide to pronunciation the words are broken up into syllables, with accent marks. Where this does not make the pronunciation evident, parenthetical phonetic spellings are provided. The words are printed in large bold-face type. Many tables and lists are included, with a two-page index to them. There are 45 plates, many in color.

In all, the book is beautifully printed, well made, reasonable in price, and unhesitatingly recommended by the reviewer.

Fertilization. By Lord Rothschild. 145 pages. New York, 1956, John Wiley & Sons, Inc. $3.50.

This short text of 142 pages is laden with scientific experiments and their results. Evidence not only is presented in fine detail, but also is analyzed and evaluated. The book contains 11 pages of bibliography with 45 references per page, 8 pages of plant and

animal index, and 7 pages of general index. It is the work of an advanced scholar, and therefore not readily understood by the average student. The opening sentence in the author's short preface reveals what is in store for the reader:

"This book is intended for those who have read, or are reading, Gray's *Experimental Cytology,* Heilbrunn's *Outline of General Physiology,* Fruton and Simonds' *General Biochemistry,* Hober's *Physical Chemistry of Cells and Tissues,* and similar textbooks."

The subject of the book is the life of the egg (usually the sea urchin) from the attachment of the fertilizing spermatozoon to the fusion or apposition of the male and female pronuclei. Every aspect of change induced by fertilization is examined thoroughly in 12 concise chapters.

Morphologic changes in the egg, as revealed by phase microscopy, are described in detail and illustrated graphically. Sperm-egg interacting substances, such as the gamone (gamete hormone) "fertilizin," are discussed at length. The immunologic reaction to fertilizin is presented; the behavior of spermatozoa in its presence is compared to serologic antigen-antibody reactions. Other sperm-egg interacting substances are enumerated, together with their biologic properties and chemical characteristics. The author points out the fact that although these enzymes dissolve membranes external to the egg, there is no evidence that they soften the plasma membrane to render it more permeable to spermatozoa. Metabolic changes induced by fertilization, as determined by oxygen uptake, respiratory quotient, and acid production, are considered and found to be variable. Owing to the impermeability of eggs (as contrasted with spermatozoa), investigation of their metabolic pathways destroys the normal egg structure and, with it, the normal egg metabolism. Knowledge of protein, carbohydrate, and lipid metabolism of eggs is reviewed and found to be meager. More is known of the inorganic chemical changes, particularly those involving potassium, calcium, and magnesium. After presenting a multitude of chemical changes found by various investigators, the author turns to a consideration of the physical chemistry of fertilization. Based upon studies with the polarizing microscope, structural changes in the cortex and protoplasm are described. Measurements of bioelectric phenomena at fertilization are examined and found to have revealed little of importance. Various experiments with cross fertilization and cross agglutination of spermatozoa are given. The author states that, although specificity in fertilization is an accepted phenomenon, no explanation of how it happens is available. Factors preventing supernumerary fertilization are indicated. The relationship between sperm density and seed and egg size to polyspermy is expressed in a mathematical formula. Other formulas are given for the calculation of the probability of a successful sperm-egg collision.

The author brings the book to a close with the very short final chapter called "Conclusion," in which he lists the subjects worthy of further investigation.

Human Ovulation and Fertility. By E. J. Farris. 159 pages. Philadelphia, 1956, J. B. Lippincott Company. $6.50.

Written by a recognized authority on the subject, the statements and conclusions of this book are quite well documented. The predominating theme is the reliability of the rat ovarian hyperemia test for the timing of ovulation. This information is not only of academic interest, but is also useful as a guide for the control of conception.

The correlation between the rat hyperemia test and other methods of determining ovulation is adequately discussed. The author does not believe that the basal body temperature shift is a reliable method for determining ovulation.

There will be some disagreement as to the advisability of thyroid therapy or roentgen ray for the correction of infertility both because of their questionable value and their possible threats.

The book is filled with tables and statistics which make reading difficult for the busy clinician, but it is valuable as a reference.

Synopsis of Gynecology. By R. J. Crossen. Fourth edition. 255 pages with 132 illustrations. St. Louis, 1956, The C. V. Mosby Company. $5.25.

This pocket-size book based upon the author's textbook, *Diseases of Women,* is a handy reference, particularly for house staff members and medical students. This edition has brought the *Synopsis* up to date, particularly in the fields of endocrinology and therapeutics.

The chapter, "Gynecologic Examination and Diagnosis," is worthy of special praise, for it deals in great detail with all aspects of this important subject. Newcomers to the field of gynecology should spend enough time reading this section to absorb it completely.

As would be expected, all readers will not agree with each aspect of therapy. One of the points of contention will be the advocation of radiotherapy for benign uterine bleeding. Certainly, the student should realize that there is much disagreement about this form of treatment; many authorities would strongly condemn its use.

The chapter on malignant disease of the uterus is short and could advantageously be enlarged. It can serve only as a springboard for the student and is too sketchy for house staff officers.

The chapter dealing with malformations is quite complete for a small book. However, the portion of the chapter that considers pseudohermaphroditism does not mention the important role of the sex chromosome in determining the sex of the individual.

The Sexual Responsibility of Woman. By M. Davis. 299 pages. New York, 1956, The Dial Press. $4.00.

There is disparity, from the reviewer's point of view, between the presumptuous title of this book and the superficial treatment of the subject matter.

Miss Davis has attempted a simplified, frank presentation of a very complicated subject, much of which should be discussed in an individual, personal manner by a qualified person in an office. Such a subject matter, in written form, may well provoke untoward reaction and anxiety in individuals.

What she does have to say, however, Miss Davis expresses in understandable lay language, in an interesting literary style.

Chapters 11 and 13 on "Protection From Pregnancy: Contraception and Family Planning" and "Sex Hygiene and Health" are treated very well, and do contain several valuable and significant suggestions.

The etiology of frigidity, including a discussion of the pubococcygeus versus the cerebral reflexes, is dealt with in an organized but inadequate fashion.

Quantitatief Serumeiwitonderzoek bij Zwangerschapstoxaemieen met Behulp van de Papierelectrophorese. By A. Bronsema. 136 pages with 21 illustrations. Groningen, 1956, Bronsema's Drukkerij, N. V.

The author fractionated the serum proteins, by means of paper electrophoresis, in 12 normal nonpregnant women, 7 normal women in the last trimester of pregnancy, and 13 patients with toxemia of pregnancy. In some of the patients serial measurements were made over periods of several weeks and post partum.

As found by others using electrophoretic techniques, the drop of about 1 Gm. of serum protein per 100 ml. in pregnancy is accounted for by the decrease in albumin. In toxemia there is a still greater diminution in albumin and most of the globulins show slight increases over the already slightly increased values in normal pregnancy. Proteinuria was associated with significant alterations in the serum protein pattern. The variations in toxemia have little, if any, value in prognosis.

Following pregnancy, about six weeks is required for the re-establishment of normal nonpregnancy values.

There is a good review of the literature, with tabulations of reported serum protein concentrations and fractionations by various methods.

Le Liquide amniotique (système amniotique): Étude clinique, biologique et physico-chemique. By F. Hannon, M. Coquoin-Carnot, and P. Pignard. 176 pages with 5 illustrations. Paris, 1955, Masson et Cie.

This is a partial review of the literature dealing with amniotic fluid. The first three chapters are concerned with clinical aspects, such as premature rupture of the membranes and induction of labor by their artificial rupture. The succeeding chapters are concerned with fetal urination, intrauterine respiration, fetal distress as evidenced by passage of meconium, fetal death, polyhydramnios and fetal malformations, and prolonged pregnancy.

The second section reviews biological and physicochemical studies of the amniotic fluid, touching upon embryology, histology, histophysiology (hormonal effects), and a smattering of histochemistry. One chapter discusses the volume and circulation of the amniotic fluid and another some of the chemical analyses that have been made.

The authors' contribution consists in bringing together many data from the literature and speculations, some of which are rather weak. For instance, in arguing against fetal urination they write that (a) the anal sphincter normally does not allow passage of meconium, and, by analogy, the bladder sphincter may not allow urination; (b) inasmuch as the fetus drinks amniotic fluid, fetal urination would result in toxicity and uremia. (Where is the placenta in this argument?)

There is an eight-page list of references.

Clinical Urology, Volumes I and II. By O. S. Lowsley, and T. J. Kirwin. Third Edition. 985 pages with 599 illustrations. Baltimore, 1956, Williams & Wilkins Company. $32.50.

This edition of *Clinical Urology* by the late Oswald S. Lowsley and Thomas J. Kirwin is an important contribution by two of the most experienced surgeons, teachers, and investigators of urologic practice. A great deal of the text is expressed in the light of their experiences which have been extensive enough to permeate all of the book's sections. In fact, one of the few shortcomings of this text is that emphasis is on the theories and procedures originated by the authors, perhaps to the exclusion of procedures of equally wide acceptance.

This revision of the last edition of 1944 includes important and useful innovations in urologic theory and practice. The book's format places the text in three columns across large pages (8½ × 11). In order to get all the text into two volumes, the type, unfortunately, is small and may prove difficult for some readers. Mr. William P. Didusch's illustrations are as always an asset to any publication. Their graphic and life-like qualities greatly amplify the text.

In instances where the urology and gynecology find common interests, there is very ample presentation. Disease of the female urethra and bladder, treatment of urinary incontinence and injuries of the ureter are lucidly discussed in their theoretical and practical aspects.

Hormones and the Aging Process. By E. T. Engle, and G. Pincus. 323 pages. New York, 1956, Academic Press, Inc. $8.50.

Papers and discussions presented at a meeting sponsored by G. D. Searle and Company at Arden House, Harriman, N. Y., compose this book.

Because a larger percentage of the population is reaching old age, geriatrics is becoming more important. As people live longer the incidence of cancer becomes greater and the role of the steroids, more important. To these subjects, the greatest portion of the book is devoted.

Although at first glance the book seems to contain too much laboratory and theoretical material, there is also an abundance of practical clinical information. As a reference which focuses attention on the latest research, the book is valuable. It is not intended as a text.

Each section is presented by an outstanding authority in the field and is discussed most informatively. The reviewer was especially impressed with the honesty and freshness of point of view of all of the participants. This is noteworthy in the field of endocrinology.

Atlas of Exfoliative Cytology, Supplement I. By G. N. Papanicolaou. Cambridge, 1956, published for the Commonwealth Fund by Harvard University Press. $4.00.

Dr. Papanicolaou, the dean of exfoliative cytologists, has added to the value of his *Atlas of Exfoliative Cytology* by this supplement, the main contribution of which is the correlation of the histopathology with cytology, a most needed link in the proper understanding and interpretation of smears. The illustrations are superb.

Practical Endocrinology. By Lewis M. Hurxthal. 318 pages with 17 illustrations. New York, 1956, McGraw-Hill Book Company. $7.00.

This book is intended for use by the general practitioner who, despite his need for medical information, has little time to read. It does not contain elaborate discussion of theory. The material is presented clearly and not too technically.

Beginning with a chapter on "Endocrine Disorders of Infancy and Childhood" and continuing with chapters devoted to each of the specific endocrine glands, the book concludes with a chapter dealing with steroid hormones and their use in general practice. In chapters devoted to the specific endocrine glands, major disorders and diseases are discussed in regard to diagnosis and treatment. A short differential diagnosis is usually included.

The chapter on office laboratory techniques is inadequate for the most part, and includes tests which are too complex. For example, I wonder how many office laboratories of general practitioners are equipped to assay urinary ketosteroids.

The intricate subject of hormones in the practice of medicine is crowded into 29 pages, running the gamut from eye diseases to hay fever. Estrogen therapy, the subject about which the general practitioner would need the most help, is confined to the last page of the chapter.

This handbook falls far short of what the general practitioner would hope to find in a review of practical endocrinology.

Treatment of Heart Disease. By H. Gross, and A. Jezer. 549 pages with 91 figures. Philadelphia, 1956, W. B. Saunders Company. $13.00.

By request of the Editor, this review will be confined to the section on pregnancy in relation to heart disease. As it happens, this is one of the least felicitous portions of the book. Here, the physiology is out of date. For instance: "The work of the heart... [reaches] a maximum about two to three weeks before term" (p. 21) and "diminishes with descent of the fetal head" (p. 437). The "reduction (sic) in vital capacity may contribute to an increase in cardiac work" (p. 428). "Systolic and diastolic [blood pressures in pregnancy] are increased, the diastolic slightly more than the systolic. The pulse pressure is also increased" (p. 427—internal contradiction and if the pressure does change in pregnancy, the modern consensus is that it falls, with the diastolic showing the greater drop). The values for arteriovenous oxygen differences in pregnancy go back 20 years, to the acetylene method for measuring cardiac output. Some of the circulatory changes are explained on the basis of the hypothesis that the placenta is an arteriovenous shunt. Possibly it is, but this is not so certain as the authors imply. Seven of the 11 references to the physiology of the heart and circulation are to papers published before 1940 and the blood volume changes specified were published in 1915. Exactly half of all references antedate 1940. Toxemias of pregnancy are divided into two groups: (a) nephritic and (b) pre-eclampsia, eclampsia, and recurring toxemia.

The section on "Prophylaxis of Cardiac Insufficiency" is insufficient by way of omission, for no mention is made of the signs of decreasing cardiac reserve or what to do

about it when it is detected. Later on the authors do say something about the effect of older age on prognosis and their recommended care for women in Classes III and IV is therapeutic abortion. In connection with the latter, "hysterectomy" seems to be confused, repeatedly, with "hysterotomy." Also, the word "cesarean" is misspelled at least nine times.

In the management of labor, they recommend anesthesia between pains, which may be augmented by scopolamine. Scopolamine is often dangerous in patients with mitral stenosis and certainly there should be some definition of and qualification as to the anesthesia between pains. They also recommend that a sandbag be placed on the abdomen after delivery.

La Fonction Tubaire et Ses Troubles. National Society for the Study of Sterility and Fertility, 418 pages with 186 illustrations. Paris, 1955, Masson & Cie. 2,700 fr.

The contents of this book are subdivided into four parts. In each section there are nine papers.

The first section, devoted to tubal physiology, includes articles on blood supply and musculature, analysis of tubal secretions, study of tubal lymphatics, tubal physiology of domestic animals, and the fertilizing capacity of spermatozoa in experimental animals.

The second section, dealing with diagnostic tubal procedures, contains contributions on the significance and types of tubal stenosis and obstruction as revealed by tubal insufflation, the significance and interpretation of tubal oscillations, hysterosalpingography with the use of Lipiodol or a water-soluble medium, manometric control of salpingography, indications and results of culdoscopy, tubal biopsy, and histological examination of the specimen, and hydrosalpinx: its diagnosis, complications, significance, and treatment.

The third section on tubal pathology discusses tubal obstruction of gonococcal, puerperal, or postabortal origin, tubal tuberculosis, endometriosis, and spasm.

In the last section, the treatment of diseased Fallopian tubes is covered. Medical and surgical means are discussed.

The contributors to this book are all well known and their presentations are excellent.

Selected Abstracts*

Journal of Gerontology

Vol. 11, January, 1956.

*Hellbaum, A. A., Eskridge, J. B., and Payne, R. W.: The Influence of Pituitary Factors on Menopausal Vasomotor Instability, p. 58.

Hellbaum, Eskridge, and Payne: The Influence of Pituitary Factors on Menopausal Vasomotor Instability, p. 58.

An unfractionated pituitary preparation that contained both LH and FSH was administered to 14 surgically castrated women. Of these, 12 had complete relief from vasomotor instability as judged by reduction in number of flushes. One had partial relief and one noted no effect. When a pituitary preparation containing primarily LH was administered to 6 oophorectomized women, none noted any reduction in the number of flushes, but when the preparation that was administered contained primarily FSH, 3 of the 4 women so treated noted complete relief and 1 woman was partially relieved. The suggestion is made that the beneficial action of estrogens and androgens upon the vasomotor instability noted after the removal of the ovaries might be due to the release of the pituitary factor.

DAVID M. KYDD

*Titles preceded by an asterisk are abstracted below.

The Lancet

Vol. 1, Jan. 28, 1956.

*Gunther, M.: Acute Mastitis, p. 175.

*Bull, G. M., Joekes, A. M., and Lowe, K. G.: Acute Tubular Necrosis of the Kidney Following Abortion, p. 186.

Gunther: Acute Mastitis, p. 175.

There are two kinds of acute mastitis: the superficial (a Staphylococcus infection of the skin or a Montgomery tubercle which penetrates the breast) and the intramammary mastitis. In 2,701 deliveries, 129 women developed mastitis, of whom 25 had the superficial type, 109 the intramammary, and 5 both types.

All of the superficial mastitis was caused by infection with *Staphylococcus pyogenes.* Except for 4 quite small lesions, all required drainage before healing ensued. Only 1 patient with superficial mastitis had fever. Treatment included care of the skin, use of antibiotics, incision, and frequent emptying of the breast.

In intramammary mastitis, pain, lump in the breast, reduction in secretion of the affected organ, and pyrexia are characteristic; a lump and pain are always present. Seventy of the 109 patients had fever. Seventy-seven (71 per cent) recovered without residual induration, and an additional 10 did not require incision. Although most of the patients received antibiotics, 4 patients had 13 attacks with retention of milk. The attacks were treated successfully by emptying the breasts without other therapy. Inasmuch as the incidence of abscess is small, and as the blood culture remained sterile in the 5 patients from whom the blood was obtained, the author suggests the following sequence: retention of milk, high pressure, leakage or even rupture of the alveoli with extravasation of the secretion. The secretion may enter the blood stream and have a pyrogenic effect. Infection, if it occurs, appears late in the disease. Prevention requires the avoidance of engorgement of the breasts by complete emptying or by prudent use of estrogens.

DAVID M. KYDD

Bull, Joekes, and Lowe: Acute Tubular Necrosis of the Kidney Following Abortion, p. 186.

Of 13 patients who developed anuria following an abortion, 7 admitted intrauterine douching. One inserted a soap paste into the cervix, 1 inserted an instrument into the uterus, and 4 refused to disclose details. The individual patients are discussed briefly. Five patients died, and these were all found on necropsy to have acute tubular necrosis. However, a serious infection was found in 3 of these fatal cases.

DAVID M. KYDD

Vol. 1, April 14, 1956.

*Platt, R., and Sears, H. T. N.: Reserpine in Severe Hypertension, p. 401.

*FitzGerald, T. B., and Jackson, S. H.: Afibrinogenemia in Obstetrics, p. 412.

*Savage, D.: Stress Fracture of Ribs in Pregnancy, p. 420.

Platt and Sears: Reserpine in Severe Hypertension, p. 401.

Of 41 patients with hypertension to whom only reserpine was administered, the drug was beneficial to 17, of doubtful value to 8, and of no value to 16. Of 13 patients with more severe hypertension who were given a ganglionic blocking agent in addition to reserpine, the effect of the latter drug was good in 9. Side effects were common. More than half the patients had drowsiness and nasal stuffiness and one patient became so depressed that suicide resulted. In 3 women lactation occurred.

DAVID M. KYDD

FitzGerald and Jackson: Afibrinogenemia in Obstetrics, p. 412.

Three patients with afibrinogenemia occurring in pregnancy were studied. The first patient (gravida iv, aged 39, 36 weeks pregnant) had hypertension, albuminuria, and

fever. Following delivery of a small live fetus and expression of the placenta, she had a hemorrhage which did not stop after the passage of a succenturiate lobe, and death occurred 3 hours after delivery. The blood did not clot and contained less fibrinogen than 100 mg. per cent. Hemorrhage in many organs together with some small pulmonary infarcts were found at necropsy.

The second patient (gravida ii, aged 26, 35 weeks pregnant) had abdominal pain and albuminuria. Her blood did not clot and no fibrinogen could be found in the plasma. Labor was induced but the fetus was stillborn and the placenta was delivered only after considerable difficulty. Bleeding which began at the time of delivery continued. She was given 0.75 Gm. fibrinogen and with the sixth pint of blood an additional 0.75 Gm. She improved. Bruising was not noticed after the fourth day and on the tenth day the fibrinogen concentration in the plasma was 250 mg. per cent.

The third patient (gravida iii, aged 26, 36 weeks pregnant) had abdominal pain and vaginal bleeding. Her blood did not clot and no fibrinogen was found in the plasma. She was given 0.3 Gm. of fibrinogen and 2 minutes later the concentration of fibrinogen in the plasma was 100 mg. per cent. In about 2 hours, however, this concentration fell to 46 mg. per cent. Seven hours after the membranes were ruptured, she delivered a stillborn fetus. At the time of delivery, an additional 0.45 Gm. fibrinogen was administered. No postpartum hemorrhage occurred and 2 days after delivery the concentration of fibrinogen in the plasma was 250 mg. per cent.

As far as possible, all blood evacuated from the uterus when the placenta was delivered was collected and found to contain 63 Gm. of fibrin. This large amount suggests that production of fibrinogen is unimpeded and that it is deposited in the uterus rather than in the vascular tree.

In view of the fortunate course of the third patient, the suggestion is made that fibrinogen should be given as soon as the diagnosis is made and additional amounts should be given periodically to keep pace with the defibrinogenation. A further dose should be administered at the time of delivery.

DAVID M. KYDD

Savage: Stress Fracture of Ribs in Pregnancy, p. 420.

To the 13 instances of stress fracture of the ribs in pregnancy recorded in the literature, 3 additional cases are added. In 2 of these, coughing appeared to be responsible. The third patient had no cough but developed pain in the left side in the thirty-sixth week of pregnancy and in the right side in the thirty-eighth week. When x-rayed, she was found to have a fracture of the seventh right rib and older fractures with callus formation of the sixth and seventh left ribs. After reviewing all reported cases, the author suggests that during late pregnancy the costal margin is everted and this abnormal position makes the ribs more vulnerable to shearing stress.

DAVID M. KYDD

Vol. 1, April 21, 1956.

*Dewhurst, C. J.: Diagnosis of Sex Before Birth, p. 471.

*Polak, A.: Hydrocortisone in the Prevention of Transfusion Thrombophlebitis, p. 484.

Dewhurst: Diagnosis of Sex Before Birth, p. 471.

Based on the discovery that genetic sex can be recognized by the arrangement of chromatin according to sex in the nuclei (Moore, Graham, and Barr: Surg., Gynec. & Obst. 96: 641, 1952) amniotic fluid obtained by artificial rupture of the membranes for the induction of labor or at cesarean section was examined. Although many nuclei had degenerated, in females the sex chromatin showed the typical arrangement in 25 to 40 per cent of the suitable nuclei, whereas in males less than 5 per cent of the nuclei had this arrangement. Nineteen specimens were obtained between the thirty-sixth and forty-second weeks of gestation and one at the twenty-sixth week (pre-eclamptic toxemia). In 18 cases (10 male and 8 female) the sex of the fetus was correctly foretold. In 2 cases the suitable nuclei were too few to permit any forecast. Thirteen suitable specimens

were obtained between the thirty-second and thirty-sixth weeks of pregnancy by abdominal paracentesis and the sex of the fetus was predicted correctly in each instance (6 male and 7 female). However, 7 attempts to obtain amniotic fluid by this means were unsuccessful (no fluid obtained 3 times, small amount of bloody fluid 3 times, and pure blood once). In one instance in which bloody fluid was obtained, premature labor at 36 weeks' gestation began at once. Although no serious consequences resulted and the method is reliable, the author does not believe that advance knowledge justifies the potential hazard to the fetus.

DAVID M. KYDD

Polak: Hydrocortisone in the Prevention of Transfusion Thrombophlebitis, p. 484.

To 3 patients, all in hepatic coma, a 20 per cent dextrose solution containing 0.001 per cent hydrocortisone was administered for 32, 46.5, and 63.5 hours, respectively. No clinical evidence of thrombophlebitis developed during or after the infusions. The patients died 2 hours, 12 hours, and 6 days, respectively, after infusions were discontinued. The peripheral veins were found to be normal macroscopically and microscopically.

DAVID M. KYDD

Surgery, Gynecology and Obstetrics

Vol. 102, April, 1956.

*Campos, J., and Soihet, S.: Histologic Changes in the Uterine Cervix During Pregnancy and the Diagnosis of Carcinoma in Situ, p. 427.

Campos and Soihet: Histologic Changes in the Uterine Cervix During Pregnancy and the Diagnosis of Carcinoma in Situ, p. 427.

A histological study was made of cervical biopsies obtained from 200 pregnant women during labor or immediately post partum. Biopsies were classified as follows:

Group A showed changes similar or identical to carcinoma in situ and constituted atypical metaplasia of the endocervix.

Group B showed hyperplasia of the basal-cell layer and increase in size of nuclei without presence of atypical nuclei.

Group C showed moderate hypertrophy of the ectocervical epithelium and hyperplasia of the basal-cell layer, the hyperplastic zone not exceeding one-third the thickness of the epithelial layer.

Group D showed no characteristic epithelial changes.

The distribution of the cases was 9.0 per cent in Group A, 8.5 per cent in Group B, 37.5 per cent in Group C, and 45.0 per cent in Group D. A follow-up examination at six weeks was done on all patients in Groups A and B (18 and 17, respectively) and on 15 patients from Group C. In cases where alterations were present on the second examination, a third series of biopsies was taken 4 to 6 weeks after the second.

Ectocervical squamous epithelium was increased in thickness in 27.8 per cent of cases in Group A, 70.5 per cent in Group B, 53.0 per cent in Group C, and 4.0 per cent in Group D. The high percentages found lead one to think that this change in pregnancy is caused by high estrogen levels.

Hyperplasia of the basal-cell layer was found in 63.0 per cent of the cases. This incidence declined to 18.1 per cent after 6 weeks. Loss of cellular stratification was found in 10.0 per cent of the cases, most of them in Group A. In 14.5 per cent of the cases there was an increase in the size of the nuclei of ectocervical or endocervical squamous epithelium. This increase was absent in all cases after 12 weeks. Nuclear hyperchromatism appeared in the cells of the endocervix in 10.0 per cent. This also disappeared 12 weeks after delivery.

In 10 women (5.0 per cent) the alterations of the epithelial morphology were exactly similar to those of carcinoma in situ. In 4 of them there was suggestive incipient infiltration of the stroma. Since a follow-up of these patients did not show changes at 6 and 12 weeks, it was concluded that these changes were due to pregnancy.

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1. Shook, D. M.: Am. Pract. & Digest Treat. 7:917 (June) 1956.
2. Schneeberg, N. G.; Perczek, L.; Nodine, J. H., and Perloff, W. H.: J.A.M.A. *161*:1062 (July 14) 1956.

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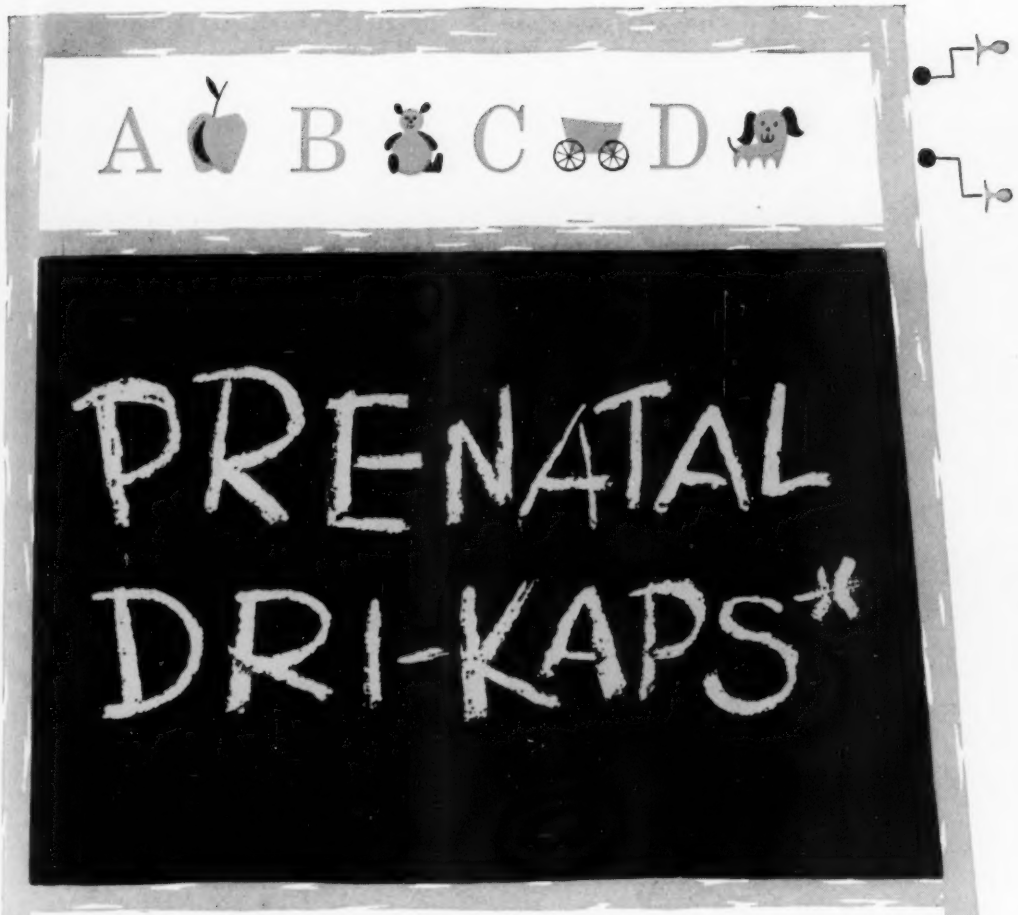

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1. Tompkins, W. T.: in Modern Nutrition in Health and Disease, ed. by Wohl, M. W. and Goodhart, R. S., Lea & Febiger, Philadelphia, 1955. p. 885.

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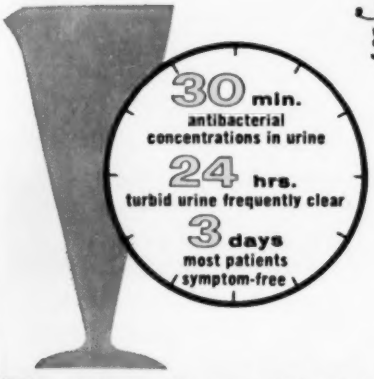

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*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956.

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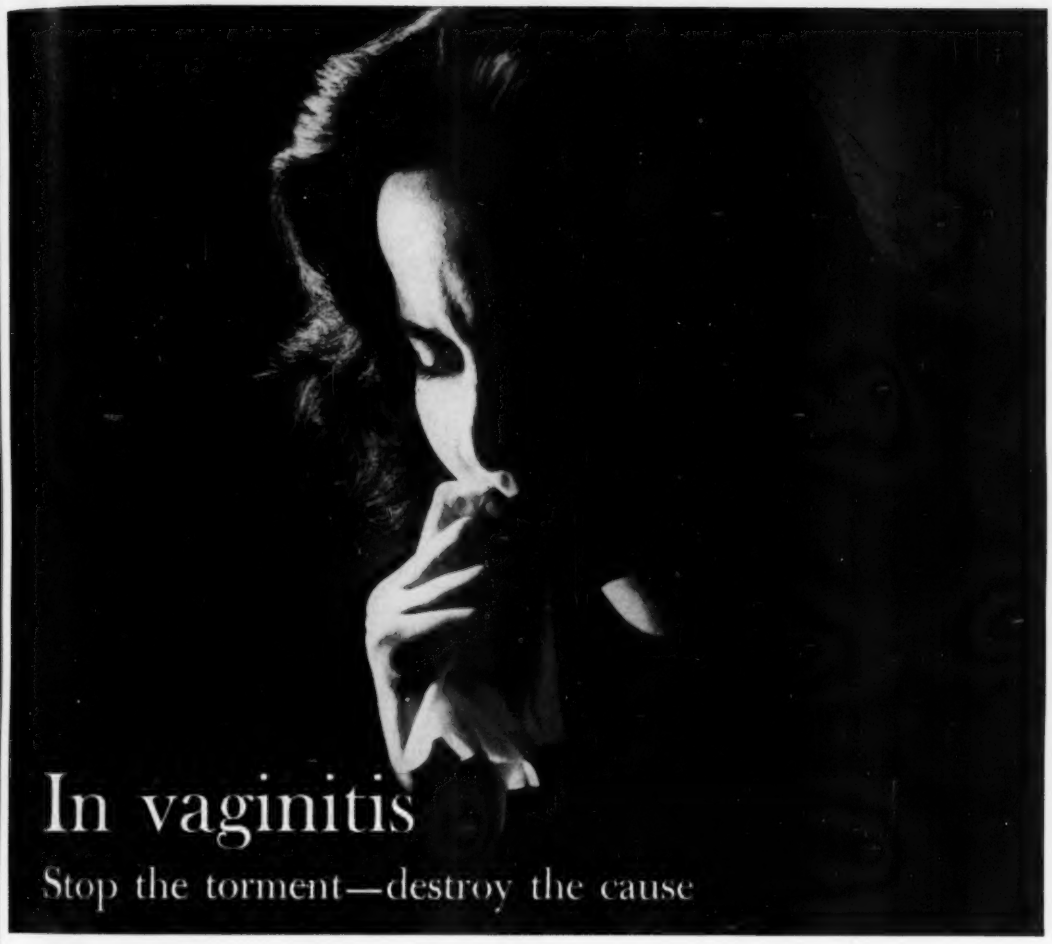

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(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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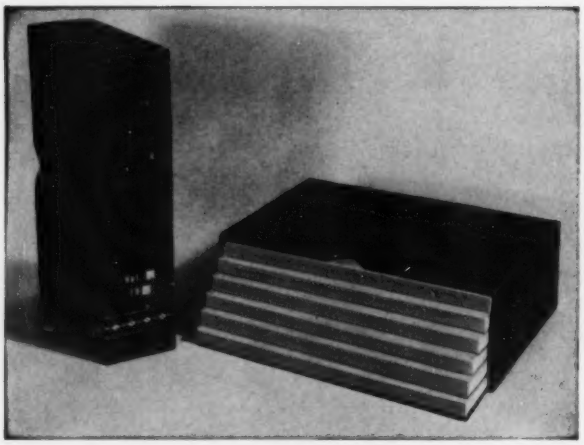

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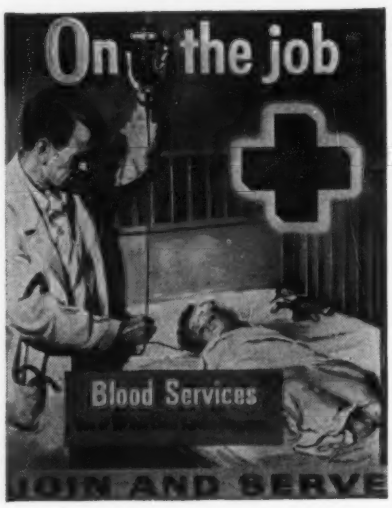

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